

From the INTERNATIONAL BUREAU

**PCT**

**NOTIFICATION OF ELECTION**

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 03 May 2000 (03.05.00)	
<b>International application No.</b> PCT/EP99/07389	<b>Applicant's or agent's file reference</b> H20058C5MN
<b>International filing date (day/month/year)</b> 23 September 1999 (23.09.99)	<b>Priority date (day/month/year)</b> 30 September 1998 (30.09.98)
<b>Applicant</b> DELANSORNE, Rémi et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
28 March 2000 (28.03.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b>  Claudio Borton  Telephone No.: (41-22) 338.83.38
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## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>H20058C5MN</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 99/ 07389</b>	International filing date (day/month/year) <b>23/09/1999</b>	(Earliest) Priority Date (day/month/year) <b>30/09/1998</b>
Applicant <b>LABORATOIRE THERAMEX et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

**4. With regard to the title,**

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

**5. With regard to the abstract,**

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No.

PC 17/20 99/07389

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 A61K38/09 A61K47/40

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	<p>EP 0 308 181 A (NOVO INDUSTRI AS)          22 March 1989 (1989-03-22)          abstract</p> <p>column 1, line 3 - line 9          column 3, line 8 - line 37          column 3, line 54 - column 4, line 22          column 4, line 59 - line 64          claims 1,5-7,12,13</p> <p>---          -/--</p>	<p>1,11-13,          21,32-34          2-12,          14-20,          22-33</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

21 January 2000

Date of mailing of the international search report

28/01/2000

Name and mailing address of the ISA

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Authorized officer

Stein, A

## INTERNATIONAL SEARCH REPORT

Intern. Application No.

PCT/ 99/07389

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 842 946 A (THERAMEX) 20 May 1998 (1998-05-20) cited in the application abstract page 3, line 38 -page 6, line 45 page 11, line 15 -page 12, line 46 page 20, line 30 -page 27, line 20 claims 1-20 ----	2-10, 14-20, 22-31
Y	WO 95 07076 A (BOLE VUNDUK BREDA ;FERCEJ TEMELJOTOV DARJA (SI); LEK TOVARNA FARMA) 16 March 1995 (1995-03-16) page 1, line 5 - line 20 page 4, line 9 - line 30 page 5, line 18 -page 6, line 7 page 8, line 12 - line 16 ----	11,12, 32,33
X	US 4 659 696 A (HIRAI SHIN-ICHIRO ET AL) 21 April 1987 (1987-04-21) abstract column 1, line 19 - line 42 column 3, line 12 - line 48 column 4, line 22 - line 41 column 6, line 42 - line 64 column 9, line 15 - line 49 column 10, line 64 -column 11, line 19 examples 3-5,9,12 claims 1,2,5,6,8,10-13,16,19,21 ----	1-7,13, 21-28
X	EP 0 839 525 A (TAKEDA CHEMICAL INDUSTRIES LTD) 6 May 1998 (1998-05-06) page 2, line 49 -page 3, line 20 page 5, line 6 -page 7, line 26 page 9, line 43 - line 51 page 10, line 27 - line 33 page 13, line 41 - line 49 claims 10-16 -----	1-7,13, 22-28,33

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07389

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0308181	A	22-03-1989	AU 2481688	A 17-04-1989
			CN 1031940	A 29-03-1989
			CS 8806143	A 14-08-1990
			DD 282396	A 12-09-1990
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			JP 3502920	T 04-07-1991
			NO 901161	A 13-03-1990
			PT 88490	A, B 01-10-1988
			YU 173088	A 30-06-1990
EP 0842946	A	20-05-1998	AU 5481798	A 03-06-1998
			CZ 9901728	A 11-08-1999
			WO 9821229	A 22-05-1998
			EP 0937101	A 25-08-1999
			NO 992298	A 08-07-1999
WO 9507076	A	16-03-1995	SI 9300470	A 30-04-1995
			AU 7511694	A 27-03-1995
			US 5840714	A 24-11-1998
US 4659696	A	21-04-1987	JP 1812631	C 27-12-1993
			JP 5024129	B 06-04-1993
			JP 59148717	A 25-08-1984
			JP 1593382	C 14-12-1990
			JP 2019092	B 27-04-1990
			JP 58189118	A 04-11-1983
			CA 1218606	A 03-03-1987
			EP 0094157	A 16-11-1983
EP 0839525	A	06-05-1998	CA 2219698	A 30-04-1998
			JP 10182496	A 07-07-1998



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : <b>A61K 38/09, 47/40</b>	<b>A1</b>	(11) International Publication Number: <b>WO 00/18423</b> (43) International Publication Date: <b>6 April 2000 (06.04.00)</b>
<p>(21) International Application Number: <b>PCT/EP99/07389</b></p> <p>(22) International Filing Date: <b>23 September 1999 (23.09.99)</b></p> <p>(30) Priority Data: <b>98402403.4</b>      <b>30 September 1998 (30.09.98)</b>      <b>EP</b></p> <p>(71) Applicant (for all designated States except US): <b>LABORATOIRE THERAMEX [MC/MC]; 6, avenue Prince Héréditaire Albert, MC-98000 Monaco (MC).</b></p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): <b>DELANSORNE, Rémi [FR/FR]; 7bis, avenue Edith Cavell, F-06000 Nice (FR). BONNET, Paule [FR/FR]; Chemin Glena, 37, route de Sospel, F-06500 Menton (FR). PARIS, Jacques [FR/FR]; 31, avenue Cap de Croix, Bât. E1, F-06100 Nice (FR).</b></p> <p>(74) Agents: <b>NEVANT, Marc et al.; Cabinet Beau de Loménie, 158, rue de l'Université, F-75340 Paris Cedex 07 (FR).</b></p>		<p>(81) Designated States: <b>AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</b></p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: <b>PHARMACEUTICAL COMPOSITIONS BASED ON ALPHA-CYCLODEXTRIN FOR THE ORAL ADMINISTRATION OF LH-RH ANALOGUES</b></p> <p>(57) Abstract</p> <p>The invention relates to the use of <math>\alpha</math>-cyclodextrin or a derivative thereof for the preparation of pharmaceutical compositions for the oral administration of LH-RH peptide analogues. The invention also relates to oral pharmaceutical compositions containing LH-RH peptide analogues in combination with <math>\alpha</math>-cyclodextrin or a derivative thereof.</p>		

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## Pharmaceutical compositions based on alpha-cyclodextrin for the oral administration of LH-RH analogues

The present invention relates to the pharmaceutical field. More specifically,  
5 the invention relates to the use of  $\alpha$ -cyclodextrin or derivatives thereof for the preparation of pharmaceutical compositions for the oral administration of LH-RH (luteinizing hormone - releasing hormone) peptide analogues. The invention also relates to oral pharmaceutical compositions containing LH-RH peptide analogues in combination with  $\alpha$ -cyclodextrin.

10 Natural and modified cyclodextrins (CDs) are well known ingredients used in a large variety of pharmaceutical preparations taking advantage of one or several of their properties relating to drug solubilization and stabilization (Loftsson and Brewster, 1996, *J. Pharm. Sci.*, **85**(10): 1017-1025) or to overall improvement of *in vivo* drug delivery (Rajewski and Stella, 1996, *J. Pharm. Sci.*, **85**(11): 1142-1169).  
15 CDs are cyclic oligosaccharides containing at least 6  $\alpha$ -D-(+)-glucopyranose units attached by  $\alpha$ (1-4) glucoside bonds (Nash, *Handbook of Pharmaceutical Excipients*, ed. by Wade and Weller, 1994, American Pharmaceutical Association, Washington, and The Pharmaceutical Press, London, pp 145-148); the three most common CDs are  $\alpha$ -,  $\beta$ - and  $\gamma$ -CD which consist of 6, 7 and 8 sugar units, respectively. Numerous  
20 derivatives of each type of CD can be obtained by random or controlled modifications of one, several or all free hydroxyl groups of the sugar moities.

LH-RH is a neurohormone produced by hypothalamic neurons and secreted in the pituitary portal vasculature to stimulate the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) by the pituitary gland. In turn, LH and FSH  
25 regulate the endocrine and germinal functions of the ovary in the female and of the testis in the male. LH-RH is a peptide of the following structure: pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH<sub>2</sub>. Numerous normal or reduced-size, linear or cyclic peptide analogues of LH-RH incorporating natural, unusual or chemically-modified amino-acids have been synthesized over the years to yield potent agonist or  
30 antagonistic properties (Karten and Rivier, 1986, *Endocr. Rev.*, **7**(1): 44-66; Dutta, 1988, *Drugs of the Future*, **13**(8): 761-787; Kutscher et al., 1997, *Angew. Chem. Int. Ed. Engl.*, **36**: 2148-2161). Due to their total or partial peptide structure, however, all these analogues show poor oral bioavailability and bioactivity.

To date, only non-oral administration of LH-RH peptide analogues, has been  
35 reported. For example, Matsubara et al. (1996, *J. Pharm. Sci.*, **84**(11) : 1295-1300) describe a nasal formulation of buserelin, based on dimethyl- $\beta$ -CD, with improved bioavailability.



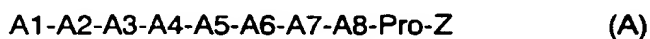
There is therefore a need, for the patients' comfort, to provide formulations which enable the oral administration of LH-RH peptide analogues.

It has now surprisingly been found that  $\alpha$ -CD or its derivatives, enhance the biological activity of LH-RH peptide analogues when orally administered.

5 Thus, according to one of its feature, the invention relates to the use of  $\alpha$ -cyclodextrin or derivatives thereof for the preparation of pharmaceutical compositions for the oral administration of LH-RH peptide analogues.

Examples of LH-RH peptide analogues which can be used within the scope of the invention include those described in International patent applications  
10 WO 98/21229 and WO 98/55505, the content of which is incorporated by reference, as well as standard agonists and antagonists of LH-RH, such as for example buserelin, nafarelin, leuprorelin, goserelin, histrelin, triptorelin, deslorelin, lutrelin, avorelin, cetorelix, antide, ganirelix, azaline B, antarelix, detirelix, ramorelix, teverelix or abarelix.

15 Preferably, these peptide analogues have the formula (SEQ ID N° : 1) :



in which :

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof such as AcPro, ForPro, OH-Pro, Ac-OH-Pro, dehydro-Pro or Ac-dehydro-Pro ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an aromatic D-amino acid which may be acylated,  
20 such as D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-diphenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe, D-HPhe, D-Tyr, D-HTyr, and D-Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, nitro or trifluoromethyl groups;

25 - A2 is a direct bond ; His ; or an aromatic D-amino acid such as D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-diphenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe, D-HPhe, D-Tyr, D-HTyr and D-Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, nitro or trifluoromethyl groups;

30 - A3 is an aromatic L- or D-amino acid such as Phe, HPhe, Tyr, HTyr, Trp, 2MeTrp, Nal, 1Nal, diphenyl-Ala, Bal, Pal, 4Pal or Qal, where Phe, HPhe, Tyr, HTyr and Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, nitro or trifluoromethyl groups;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu<sup>t</sup>), Ser(OBzl) or Thr;

- A5 is an aromatic L-amino acid such as Phe, HPhe, Tyr, HTyr, Trp, 2MeTrp, Nal, 1Nal, diphenyl-Ala, Bal, Pal, 4Pal or Qal, where Phe, HPhe, Tyr, HTyr and Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, nitro or trifluoromethyl groups and/or N-alpha-substituted by a (C<sub>1</sub>-C<sub>4</sub>)alkyl group optionally substituted by one or several fluorine atoms ; or a basic L- or D-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe or ACha, where Arg and HArg may be N-substituted by a (C<sub>1</sub>-C<sub>6</sub>)alkyl or a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl group on one or both nitrogen atoms, and where Orn, Lys, HLys, APhe and ACha may be N-substituted by one or two (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl groups, or by an aminotriazolyl or a nicotinoyl, isonicotinoyl, 6-methyl-nicotinoyl, glycyl-nicotinoyl, nicotinyl-azaglycyl, furyl, glycyl-furyl, furyl-azaglycyl, pyrazinyl, pyrazinyl-carbonyl, picolinoyl, 6-methyl-picolinoyl, shikimyl, shikimyl-glycyl, Fmoc or Boc group;

- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu<sup>t</sup>) ; D-Asp(OBu<sup>t</sup>) ; D-Glu(OBu<sup>t</sup>) ; D-Thr(OBu<sup>t</sup>) ; D-Cys(OBu<sup>t</sup>) ; D-Ser(OR<sub>1</sub>) where R<sub>1</sub> is a sugar moiety ; an aza-amino acid such as azaGly or azaAla ; D-His which may be substituted on the imidazole ring by a (C<sub>1</sub>-C<sub>6</sub>)alkyl, a (C<sub>2</sub>-C<sub>7</sub>)acyl or a benzyl group ; an aliphatic D-amino acid with a (C<sub>1</sub>-C<sub>8</sub>)alkyl or a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl side chain such as D-Ala, D-Abu, D-Aib, D-3Aib, D-Val, D-Nva, D-Leu, D-Ile, D-Tle, D-Nle, D-Hol, D-Npg, D-CPa, D-Cpa, D-Cba or D-Cha ; an aromatic D-amino acid such as D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-diphenyl-Ala, D-anthryl-Ala, D-phenanthryl-Ala, D-benzhydryl-Ala, D-fluorenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe, D-HPhe, D-Tyr, D-HTyr and D-Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, nitro or trifluoromethyl groups ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic L- or D-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe or ACha, where Arg and HArg may be N-substituted by a (C<sub>1</sub>-C<sub>6</sub>)alkyl or a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl group on one or both nitrogen atoms, and where Orn, Lys, HLys, APhe and ACha may be N-substituted by one or two (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl groups, or by an aminotriazolyl or a nicotinoyl, isonicotinoyl, 6-methyl-nicotinoyl, glycyl-nicotinoyl, nicotinyl-azaglycyl, furyl, glycyl-furyl, furyl-azaglycyl, pyrazinyl, pyrazinyl-carbonyl, picolinoyl, 6-methyl-picolinoyl, shikimyl, shikimyl-glycyl, Fmoc or Boc group;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms such as Ala, Abu, Aib, 3Aib, Val, Nva, Leu, Ile, Tle, Nle, Hol, Npg, Cpa,

Cba, Cha or Ada, which may be N-alpha-substituted by a (C<sub>1</sub>-C<sub>4</sub>)alkyl group optionally substituted by one or several fluorine atoms ;

- A8 is a basic L- or D-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe or ACha, where Arg or HArg may be N-substituted by a (C<sub>1</sub>-C<sub>6</sub>)alkyl or a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl group on one or both nitrogen atoms, and where Orn, Lys, HLys, APhe or ACha may be N-substituted by one or two (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl groups, or by an aminotriazolyl or a nicotinoyl, isonicotinoyl, 6-methyl-nicotinoyl, glycylic-nicotinoyl, nicotinyl-azaglycyl, furyl, glycylic-furyl, furyl-azaglycyl, pyrazinyl, pyrazinyl-carbonyl, picolinoyl, 6-methyl-picolinoyl, shikimyl, shikimyl-glycyl, Fmoc or Boc group;

- Z is GlyNH<sub>2</sub> ; D-AlaNH<sub>2</sub> ; azaGlyNH<sub>2</sub> ; or a group -NHR<sub>2</sub> where R<sub>2</sub> is a (C<sub>1</sub>-C<sub>4</sub>)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl;

as well as their pharmaceutically acceptable salts.

In the present description the term "(C<sub>1</sub>-C<sub>4</sub>)alkyl" denotes methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl and t-butyl groups.

The term "(C<sub>1</sub>-C<sub>6</sub>)alkyl" denotes methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, s-pentyl, t-pentyl and hexyl groups.

The term "(C<sub>1</sub>-C<sub>8</sub>)alkyl" denotes methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, s-pentyl, t-pentyl, hexyl, heptyl and octyl groups ;

The term "(C<sub>1</sub>-C<sub>4</sub>)alkoxy" denotes a group -OR where R is a (C<sub>1</sub>-C<sub>4</sub>)alkyl.

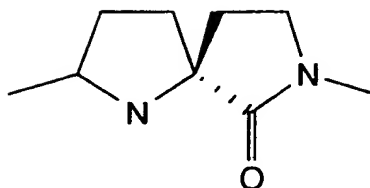
The term "(C<sub>2</sub>-C<sub>7</sub>)acyl" denotes a group -COR where R is a (C<sub>1</sub>-C<sub>6</sub>)alkyl.

The term "(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl" denotes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups.

The term "sugar moiety" denotes D- or L-pentoses or hexoses and their amino-derivatives.

The term "LH-RH analogues" denotes peptides in which at least one amino acid has been modified in the sequence of LH-RH.

The term "(S)spirolactam-Pro" denotes the residue of the formula :



The term "oral administration" denotes the delivery of the peptide analogues of the invention to the gastrointestinal tract by means of an oral formulation or composition.

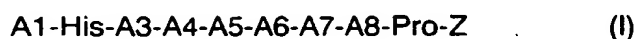
- 5       Peptidomimetic analogues of LH-RH defined by the absence of at least one peptide amide bond, as exemplified in the latest review by Kutscher et al. (1997, *Angew. Chem. Int. Ed. Engl.*, **36**: 2148-2161), are not considered within the scope of the present invention.

10       In the present description and in the claims, the following abbreviations are used :

Abu : 2-aminobutyric acid	Ac : acetyl
ACha : aminocyclohexylalanine	Aib : 2-aminoisobutyric acid
3Aib : 3-aminoisobutyric acid	Ala : alanine
AlaNH <sub>2</sub> : alaninamide	APhe : p-aminophenylalanine
Arg : arginine	Asp : aspartic acid
azaAla : aza-alanine	azaGly : aza-glycine
azaGlyNH <sub>2</sub> : azaglycinamide	Bal : benzothienylalanine
Boc : <i>tert</i> -butoxycarbonyl	Cba : cyclobutylalanine
Cha : cyclohexylalanine	Cit : citrulline
CPa : cyclopropylalanine	Cpa : cyclopentylalanine
Fmoc : fluorenylmethoxycarbonyl	For : formyl
Glu : glutamic acid	Gly : glycine
GlyNH <sub>2</sub> : glycineamide	HArg : homoarginine
HCit : homocitrulline	His : histidine
HLys : homolysine	Hol : homoleucine
Ile : isoleucine	lprLys : N <sup>ε</sup> -isopropyllysine
Leu : leucine	Lys : lysine
MeSer : N-methylserine	Met : methionine
Nal : 3-(2-naphtyl)alanine	1Nal : 3-(1-naphtyl)alanine
NEt : N-ethylamide	NicLys : N <sup>ε</sup> -nicotinoyllysine

Nle : norleucine	Npg : neopentylglycine
Nva : norvaline	OBu <sup>t</sup> : <i>tert</i> -butoxy
OBzl : benzyl ester	Orn : ornithine
Pal : 3-(3-pyridyl)alanine	pClPhe : 3-(4-chlorophenyl)alanine
Pen : penicillamine	pGlu : pyroglutamic acid
Phe : phenylalanine	Pro : proline
Qal : 3-(3-quinolyl)alanine	Sar : sarcosine
Ser : serine	(S-Me)Pen : S-methyl-penicillamine
(S-Et)Pen : S-ethyl-penicillamine	Thr : threonine
Tle : <i>tert</i> -leucine	Trp : tryptophan
Tyr : tyrosine	Val : valine
Ada : adamantylalanine	HPhe : homophenylalanine
MeNpg : N-methylnopentylglycine	4Pal : 3-(4-pyridyl)alanine
HTyr : homotyrosine	2MeTrp : 2-methyltryptophan
Bzl : benzyl	SPL : (S)spiro lactam-Pro
Asn : asparagine	MeLeu : N-methyllleucine
MeTyr : N-methyltyrosine	MeHTyr : N-methylhomotyrosine

A preferred group of peptide analogues (A) comprises the peptides of the formula (SEQ ID N° : 2) :



5 in which:

- A1 is pGlu, Sar or AcSar;
- A3 is an aromatic L-amino acid such as Phe, HPhe, Tyr, HTyr, Trp, 2MeTrp, Nal, 1Nal, diphenyl-Ala, Bal, Pal, 4Pal or Qal, where Phe, HPhe, Tyr, HTyr and Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, nitro or trifluoromethyl groups;
- 10 - A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu<sup>t</sup>), Ser(OBzl) or Thr;
- A5 is an aromatic L-amino acid such as Phe, HPhe, Tyr, HTyr, Trp, 2MeTrp, Nal, 1Nal, diphenyl-Ala, Bal, Pal, 4Pal or Qal, where Phe, HPhe, Tyr, HTyr and Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, nitro or
- 15 trifluoromethyl groups;

- A6 is Gly ; D-Pro ; (S)-spirolactam-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu<sup>1</sup>) ; D-Asp(OBu<sup>1</sup>) ; D-Glu(OBu<sup>1</sup>) ; D-Thr(OBu<sup>1</sup>) ; D-Cys(OBu<sup>1</sup>) ; D-Ser(OR<sub>1</sub>) where R<sub>1</sub> is a sugar moiety ; an aza-amino acid such as azaGly or azaAla ; D-His which may be substituted on the imidazole ring by a (C<sub>1</sub>-C<sub>6</sub>)alkyl or a benzyl group ; an aliphatic D-amino acid with a (C<sub>1</sub>-C<sub>6</sub>)alkyl or a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl side chain such as D-Ala, D-Abu, D-Aib, D-3Aib, D-Val, D-Nva, D-Leu, D-Ile, D-Tle, D-Nle, D-Hol, D-Npg, D-CPa, D-Cpa, D-Cba or D-Cha ; an aromatic D-amino acid such as D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-diphenyl-Ala, D-anthryl-Ala, D-phenanthryl-Ala, D-benzhydryl-Ala, D-fluorenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe, DHPhe, D-Tyr, D-HTyr and D-Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, nitro or trifluoromethyl groups ; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic D-amino acid such as D-Arg, D-HArg, D-Orn, D-Lys, D-HLys, D-Cit, D-HCit, D-APhe optionally substituted by an aminotriazolyl group or D-ACha, where D-Arg and D-HArg may be N-substituted by a (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl groups, or by a Fmoc or Boc group;

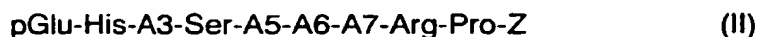
- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms such as Ala, Abu, Aib, 3Aib, Val, Nva, Leu, Ile, Tle, Nle, Hol, Npg, Cpa, Cba, Cha or Ada, which may be N-alpha-substituted by a (C<sub>1</sub>-C<sub>4</sub>)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is a basic L-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe optionally substituted by an aminotriazolyl group, or ACha;

- Z is GlyNH<sub>2</sub> ; azaGlyNH<sub>2</sub> ; or a group -NHR<sub>2</sub> where R<sub>2</sub> is a (C<sub>1</sub>-C<sub>4</sub>)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl;

as well as their pharmaceutically acceptable salts.

Among the peptide analogues of formula (I), those of the formula (SEQ ID N° : 3) :



in which:

- A3 and A5 are aromatic L-amino acids as defined for (I) ;
- A6 is as defined for (I) ;

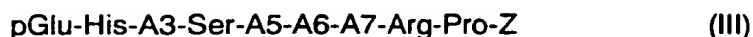
- A7 is Leu, Tle, Nle, Hol, Npg, Cha or Ada, which may be N-alpha-substituted by a methyl or ethyl group optionally substituted by one or several fluorine atoms;

- Z is as defined for (I) ;

as well as their pharmaceutically acceptable salts,

5 are preferred.

Especially preferred are the peptide analogues of the formula (SEQ ID N° ; 4) :



in which:

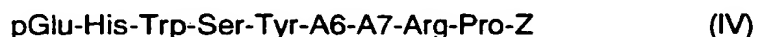
10 - A3 and A5 are each independently Phe, Tyr, Trp, 2MeTrp, HPhe, HTyr, Nal, 1Nal, Bal, Pal, 4Pal, or pClPhe ;

- A6 is (S)-spirolactam-Pro ; Gly; D-Pro ; D-Ser(OBu<sup>t</sup>) ; D-Asp(OBu<sup>t</sup>) ; D-Glu(OBu<sup>t</sup>) ; D-Thr(OBu<sup>t</sup>) ; D-Cys(OBu<sup>t</sup>) ; D-His or D-His(Bzl) ; D-Ala, D-Leu, D-Tle, D-Nle, D-Hol, D-Npg or D-Cha ; D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, 15 D-Nal, D-1Nal, D-Bal, D-Pal, D-4Pal, or D-pClPhe; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or D-APhe optionally substituted by an aminotriazolyl group ;

- A7 is Leu, Npg or Cha, which may be N-alpha-substituted by a methyl group;

- Z is GlyNH<sub>2</sub> ; azaGlyNH<sub>2</sub> or -NC<sub>2</sub>H<sub>5</sub>.

20 Also especially preferred are the peptide analogues of the formula (SEQ ID N° : 5) :



in which:

25 - A6 is (S)-spirolactam-Pro, D-Leu, D-Ala, D-Nal, D-Phe, D-Ser(OBu<sup>t</sup>) or D-Trp;

- A7 is Leu, MeLeu, Npg or MeNpg;

- Z is GlyNH<sub>2</sub> ; azaGlyNH<sub>2</sub> or -NC<sub>2</sub>H<sub>5</sub>.

The peptide analogues of formula (I) to (IV) in which A7 is Npg are especially preferred.

30 Representative peptide analogues of formula (I) to (IV) include leuprorelin, [Npg<sup>7</sup>]-leuprorelin, triptorelin, [Npg<sup>7</sup>]-triptorelin, goserelin, [Npg<sup>7</sup>]-goserelin, buserelin and [Npg<sup>7</sup>]-buserelin.

Another preferred group of peptide analogues (A) comprises the peptides of the formula (SEQ ID N° : 6) :

## A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z

(I')

in which:

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof such as AcPro, ForPro, OH-Pro, Ac-OH-Pro, dehydro-Pro or Ac-dehydro-Pro ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an aromatic D-amino acid which may be acylated, preferably acetylated, such as D-Phe, D-HPhe, D-Tyr, D-Trp, D-Nal, D-1Nal, D-diphenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe and D-Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, nitro or trifluoromethyl groups;
- A2 is a direct bond or an aromatic D-amino acid such as D-Phe, D-HPhe, D-Tyr, D-Trp, D-Nal, D-1Nal, D-diphenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe and D-Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, nitro or trifluoromethyl groups;
- A3 is an aromatic L- or D-amino acid such as Phe, HPhe, Tyr, Trp, Nal, 1Nal, diphenyl-Ala, Bal, Pal, 4Pal or Qal, where Phe and Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, nitro or trifluoromethyl groups;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu<sup>t</sup>), Ser(OBzl) or Thr;
- A5 is an aromatic L-amino acid such as Phe, HPhe, Tyr, HTyr, Trp, Nal, 1Nal, diphenyl-Ala, Bal, Pal, 4Pal or Qal, where Phe, Tyr, HTyr and Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, nitro or trifluoromethyl groups and/or N-alpha-substituted by a (C<sub>1</sub>-C<sub>4</sub>)alkyl group optionally substituted by one or several fluorine atoms; or a basic L- or D-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe or ACha, where Arg and HArg may be N-substituted by a (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl group on one or both nitrogen atoms, and where Orn, Lys, HLys, APhe and ACha may be N-substituted by one or two (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl groups, or by a nicotinoyl, isonicotinoyl, 6-methyl-nicotinoyl, glycyl-nicotinoyl, nicotinyl-azaglycyl, furyl, glycyl-furyl, furyl-azaglycyl, pyrazinyl, pyrazinyl-carbonyl, picolinoyl, 6-methyl-picolinoyl, shikimyl, shikimyl-glycyl, Fmoc or Boc group;
- A6 is Gly ; (S)-spiolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu<sup>t</sup>) ; D-Asp(OBu<sup>t</sup>) ; D-Glu(O-Bu<sup>t</sup>) ; D-Thr(O-Bu<sup>t</sup>) ; D-Cys(O-Bu<sup>t</sup>) ; D-Ser(O-R<sub>1</sub>) where R<sub>1</sub> is a sugar moiety ; an aliphatic D-amino acid with a (C<sub>1</sub>-C<sub>6</sub>)alkyl or a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl side chain such as D-Ala, D-Abu, D-Aib, D-3Aib, D-Val, D-Nva, D-Leu, D-Ile, D-Tle, D-Nle, D-Hol, D-



Npg, D-CPa, D-Cpa, D-Cba or D-Cha ; an aromatic D-amino acid such as D-Phe, D-HPhe, D-Tyr, D-Trp, D-Nal, D-1Nal, D-diphenyl-Ala, D-anthryl-Ala, D-phenanthryl-Ala, D-benzhydryl-Ala, D-fluorenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe and D-Trp may be substituted by one or more halogens, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, 5 nitro or trifluoromethyl groups ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic L- or D-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe or ACha, where Arg and HArg may be N-substituted by a (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl group on one or both nitrogen atoms, and where Orn, Lys, HLys, APhe and ACha may be N-substituted by one or two (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl groups, or by a nicotinoyl, isonicotinoyl, 6-methyl-nicotinoyl, glycyl-nicotinoyl, nicotinyl-azaglycyl, furyl, glycyl-furyl, furyl-azaglycyl, pyrazinyl, pyrazinyl-carbonyl, picolinoyl, 6-methyl-picolinoyl, shikimyl, shikimyl-glycyl, Fmoc or Boc group;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms such as Ala, Abu, Aib, 3Aib, Val, Nva, Leu, Ile, Tle, Nle, Hol, Npg, CPa, Cpa, Cba, Cha or Ada, which may be N-alpha-substituted by a (C<sub>1</sub>-C<sub>4</sub>)alkyl group optionally substituted by one or several fluorine atoms ;

- A8 is a basic L- or D-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe or ACha, where Arg and HArg may be N-substituted by a (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl group on one or both nitrogen atoms, and where Orn, Lys, HLys, APhe and ACha may be N-substituted by one or two (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl groups, or by a nicotinoyl, isonicotinoyl, 6-methyl-nicotinoyl, glycyl-nicotinoyl, nicotinyl-azaglycyl, furyl, glycyl-furyl, furyl-azaglycyl, pyrazinyl, pyrazinyl-carbonyl, picolinoyl, 6-methyl-picolinoyl, shikimyl, shikimyl-glycyl, Fmoc or Boc group;

- Z is GlyNH<sub>2</sub> or D-AlaNH<sub>2</sub>;

as well as their pharmaceutically acceptable salts.

Among the peptides of formula (I'), those of the formula (SEQ ID N° : 7):

Ac-D-Nal-D-pCIPhe-D-Pal-Ser-A5-A6-A7-A8-Pro-D-AlaNH<sub>2</sub> (II')

in which :

- A5 is Tyr, HTyr, MeTyr, MeHTyr, NicLys or IprLys;

- A6 is (S)-spirolactam-Pro, D-Arg, D-NicLys, D-IprLys, D-Cit, D-HCit or D-Asn;

- A7 is Leu, MeLeu, Npg or MeNpg;

- A8 is Arg, NicLys or IprLys;  
and their pharmaceutically acceptable salts,  
are preferred.

5 The peptide analogues of formula (I') and (II') in which A7 is Npg are especially preferred.

Representative peptide analogues of formula (I') and (II') include antide, [Npg<sup>7</sup>]-antide, cetorelix, [Npg<sup>7</sup>]-cetorelix, abarelix and [Npg<sup>7</sup>]-abarelix.

Further preferred peptide analogues comprise those of formula (A) where A6 is as defined therein except D-Asn.

10 Examples of the salts with pharmaceutically acceptable acids are those with mineral acids, such as for example the hydrochloride, hydrobromide, sulfate, phosphate, borate, hydrogensulfate, dihydrogenphosphate or nitrate, and those with organic acids, such as for example the acetate, oxalate, tartrate, succinate, maleate, fumarate, gluconate, citrate, pamoate, malate, ascorbate, benzoate, p-  
15 toluenesulfonate or naphtalenesulfonate.

Examples of the salts with pharmaceutically acceptable bases are those with alkali or alkaline earth metals such as sodium, potassium, calcium or magnesium, and those with organic bases such as amines, trometamol, N-methylglutamine, and the like.

20 The peptides used in the present invention can be prepared by the well-known techniques of peptide chemistry such as for example peptide synthesis in solution or solid phase peptide synthesis. In general, these techniques involve the stepwise addition of one or more amino acids -which may be suitably protected- to a forming peptide chain. Reference can for example be made to *Synthetic Peptides: a user's*  
25 *guide*, ed. by G.A. Grant, 1992, UWBC Biotechnical Resource Series, Washington University Press, Saint-Louis, USA.

Each molecule of  $\alpha$ -CD bears 6 primary hydroxyl groups and 12 secondary hydroxyl groups, respectively corresponding to the 6-OH and to the 2- and 3-OH groups of each of the 6 glucopyranose units. Another general aspect of the present  
30 invention concerns  $\alpha$ -CD and its derivatives which are defined as the result of chemical or biochemical modifications involving a precise or average number between 1 and 18 hydroxyl groups of the  $\alpha$ -CD molecule, in a random or regioselective fashion, with one or several different types of reactions such as oxidation, reduction, alkylation, hydroxyalkylation, esterification with organic or

mineral acids, intramolecular dehydration, tosylation followed by reductive amination or halogen substitution, sugar branching or further polymerization, and their different possible combinations and mixtures. Examples of  $\alpha$ -CD derivatives include  $\alpha$ -CD modified with one or more groups selected from methyl, carboxymethyl, ethyl, butyl, octyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, acetyl, propionyl, butyryl, succinyl, benzoyl, palmityl, sulfonyl, toluenesulfonyl, amino, aminopropyl, glucosyl, maltosyl, dimaltosyl, carboxymethyl ether, sulfobutylether, and phosphate ester.

Preferred  $\alpha$ -CD derivatives according to the invention comprise methylated  $\alpha$ -CD ; hexakis(2,3,6-tri-O-methyl)- $\alpha$ -CD, also known as "permethylated"  $\alpha$ -CD ; carboxymethylated  $\alpha$ -CD and phosphated  $\alpha$ -CD.  $\alpha$ -CD and hexakis(2,3,6-tri-O-methyl)- $\alpha$ -CD are especially advantageous when used in the preparation of the pharmaceutical compositions of the invention.

As mentioned above,  $\alpha$ -CD or its derivatives enhance the biological activity of LH-RH peptide analogues in oral pharmaceutical compositions.

Thus, according to another feature, the invention relates to oral pharmaceutical compositions which comprise as the active principle a LH-RH peptide analogue as defined above in the form of a combination with  $\alpha$ -CD or a derivative thereof, said compositions being intended to be delivered to the gastrointestinal tract.

The peptides according to the general formula (I) exert an agonist activity upon the LH-RH receptors *in vivo*, resulting in the stimulation of LH secretion by the pituitary, which, in males, stimulates the secretion of testosterone by the testis.

Adult male Sprague-Dawley rats were orally administered by gavage an oral formulation comprising leuporelin (LEU, Bachem), triptorelin (TRI, Bachem), deslorelin (DES, Saxon Biochemicals), goserelin (GOS, Saxon Biochemicals) or the other following example analogues: example 1 ([*(S)*spirolactam(Pro<sup>6</sup>, Npg<sup>7</sup>), desGly<sup>10</sup>-ProNet<sup>9</sup>]LH-RH), example 2 ([D-Ala<sup>6</sup>, Npg<sup>7</sup>, desGly<sup>10</sup>-ProNet<sup>9</sup>]LH-RH), example 3 ([Npg<sup>7</sup>]leuporelin), example 4 ([D-Phe<sup>6</sup>, Npg<sup>7</sup>, desGly<sup>10</sup>-ProNet<sup>9</sup>]LH-RH), example 5 ([Npg<sup>7</sup>]triptorelin) and example 6 ([D-Ala<sup>6</sup>, desGly<sup>10</sup>-ProNet<sup>9</sup>]LH-RH, Bachem), in combination with  $\alpha$ -CD (Sigma or Wacker Chemie). As a comparison, the same agonists have been orally administered by gavage in a standard aqueous vehicle not comprising  $\alpha$ -CD (comparative examples). For screening purposes, blood samples were drawn 2 hours after oral administration of a common dose of 2 nmoles/rat of LH-RH peptide agonists in an aqueous solution containing 10 or 100

mM of  $\alpha$ -CD (Tables 1 and 2; Figures 1, 4 and 6). For kinetic purposes, the effects of 2 nmoles/rat of example 3 with or without 100 mM of  $\alpha$ -CD were tested between 0.5 and 8 hours on plasma LH and testosterone levels (Figures 2 and 5). The influence of increasing concentrations of  $\alpha$ -CD (5%, 10% or 14%) was tested with example 2 at the dose of 5  $\mu$ g/kg 2 hours after oral administration (Figure 3). Total plasma testosterone (Diagnostic System Laboratories) and LH (Amersham Pharmacia Biotech) determinations were performed by radioimmunoassay. In screening 2-hour experiments, each group comprised between 6 and 8 rats; each time point of the kinetic study was studied on four animals.

Table 1 : stimulation of testosterone secretion

Compound without $\alpha$ -CD	total plasma testosterone (nmol/l) (m $\pm$ sem)	Compound with $\alpha$ -CD	total plasma testosterone (nmol/l) (m $\pm$ sem)
Control	8.6 $\pm$ 3.32	Control ( $\alpha$ -CD)	3.8 $\pm$ 0.66
Triptorelin	25.8 $\pm$ 3.14	Triptorelin ( $\alpha$ -CD)	61.9 $\pm$ 6.01
Leuprorelin	26.3 $\pm$ 5.77	Leuprorelin ( $\alpha$ -CD)	70.7 $\pm$ 4.06
Goserelin	21.4 $\pm$ 5.99	Goserelin ( $\alpha$ -CD)	66.5 $\pm$ 6.19
Deslorelin	9.7 $\pm$ 2.41	Deslorelin ( $\alpha$ -CD)	48.2 $\pm$ 7.29
C. ex 1	40.1 $\pm$ 6.78	Example 1	58.0 $\pm$ 8.75
C. ex 2	23.0 $\pm$ 8.54	Example 2	72.8 $\pm$ 4.64
C. ex 3	39.7 $\pm$ 8.11	Example 3	69.7 $\pm$ 3.6
C. ex 4	30.1 $\pm$ 5.86	Example 4	67.9 $\pm$ 9.11
C. ex 5	15.8 $\pm$ 4.24	Example 5	52.1 $\pm$ 6.99
C. ex 6	28.3 $\pm$ 4.56	Example 6	61.8 $\pm$ 5.10

As can be seen from the above results as well as from Figures 1-4, oral formulations with  $\alpha$ -CD significantly enhance the stimulation of testosterone secretion induced by LH-RH analogues. Especially, deslorelin alone was inactive at this threshold dose of 2 nmoles/rat, but showed a marked potency when formulated with  $\alpha$ -CD. The crucial role played by  $\alpha$ -CD is demonstrated by the concentration-dependance of its effect : combined with 10 mM  $\alpha$ -CD (0.972%), the oral activity of example 3 was not significantly improved (Figure 1) ; at 5% (51.4 mM),  $\alpha$ -CD did

enhance the stimulation of testosterone secretion induced by example 2 by oral administration, although not to the maximal level achieved with 10% (103 mM) as well as 14% (144 mM) (Figure 3).

It is also worth noting (see figures 1 and 3) that  $\beta$ -CD, hydroxypropyl- $\beta$ -CD (HP- $\beta$ -CD) and  $\gamma$ -CD have no potentiating effect on the LH-RH analogue-induced stimulation of testosterone secretion.

Table 2 : stimulation of LH secretion

Compound without $\alpha$ -CD	total plasma LH (ng/ml) (m $\pm$ sem)	Compound with $\alpha$ -CD	total plasma LH (ng/ml) (m $\pm$ sem)
Control	1.2 $\pm$ 0.11	Control ( $\alpha$ -CD)	1.1 $\pm$ 0.10
Triptorelin	1.4 $\pm$ 0.10	Triptorelin ( $\alpha$ -CD)	10.1 $\pm$ 2.54
Leuporelin	1.2 $\pm$ 0.14	Leuporelin ( $\alpha$ -CD)	12.3 $\pm$ 2.03
C. ex 1	1.5 $\pm$ 0.19	Example 1	7.1 $\pm$ 1.68
C. ex 2	1.6 $\pm$ 0.14	Example 2	19.7 $\pm$ 3.70
C. ex 3	2.2 $\pm$ 0.58	Example 3	10.9 $\pm$ 1.66
C. ex 4	1.4 $\pm$ 0.17	Example 4	16.1 $\pm$ 5.22
C. ex 5	1.4 $\pm$ 0.10	Example 5	3.2 $\pm$ 0.56

As can be seen from the above results as well as from Figures 5-6, the potentiating effect of  $\alpha$ -CD in oral formulations containing LH-RH analogues on LH release is even more pronounced than on testosterone secretion : all tested LH-RH analogues were inactive when administered alone at the same dose of 2 nmoles/rat, whereas, depending on the analogue, they induced a 3- to 16-fold increase above control levels when administered in combination with  $\alpha$ -CD.

Similar or even better results were obtained with  $\alpha$ -CD derivatives such as methylated  $\alpha$ -CD, hexakis(2,3,6-tri-O-methyl)- $\alpha$ -CD, carboxymethylated  $\alpha$ -CD or phosphorylated  $\alpha$ -CD. All  $\alpha$ -CD derivatives were purchased from Cyclolab (Budapest, Hungary). The influence of  $\alpha$ -CD derivatives were compared with that of  $\alpha$ -CD itself on the potentiation of LH-RH agonist activity of example 3 when administered by gavage to rats at the low dose of 5  $\mu$ g/kg p.o. : total testosterone plasma levels were measured 2 hours after administration (Table 3).

Table 3 : Stimulation of testosterone secretion by example 3

dose ( $\mu\text{g/kg p.o.}$ )	cyclodextrin (CD) type (concentration)	testosterone levels (ng/ml) ; ( $m \pm \text{sem}$ )	n rats
0 (control)	none	$1.0 \pm 0.17$	24
5	none	$3.4 \pm 0.79$	16
5	carboxymethylated $\alpha$ -CD (50%)	$6.9 \pm 1.62$	10
5	methylated $\alpha$ -CD (30%)	$7.1 \pm 1.59$	10
5	phosphated $\alpha$ -CD (30%)	$7.4 \pm 2.00$	10
5	$\alpha$ -CD (10%)	$10.0 \pm 1.22$	24
5	permethylated $\alpha$ -CD (15%)	$12.9 \pm 1.10$	10

The  $\alpha$ -CD derivatives tested above at least doubled the effect of example 3 by oral administration. Native  $\alpha$ -CD and its permethylated derivative appeared to be especially favorable with respectively a 2.9- and 3.8- fold enhancement of agonist activity of example 3 on testosterone at this dose level of  $5 \mu\text{g/kg p.o.}$

In a further experiment, example 3 was tested with  $\alpha$ -CD or permethylated  $\alpha$ -CD at an equal concentration of 10%. Two hours after administration, plasma LH levels were measured on eight rats per dose group (Figure 7). The  $5 \mu\text{g/kg p.o.}$  dose of example 3 alone was inactive on LH levels at this time point, and 10 and  $20 \mu\text{g/kg p.o.}$  were clearly threshold doses in these experimental conditions.

Combination of example 3 with 10%  $\alpha$ -CD resulted in slight but significant stimulations at 5 and  $10 \mu\text{g/kg p.o.}$ , and in a much greater effect at  $20 \mu\text{g/kg p.o.}$  when compared with example 3 alone (over 5-fold enhancement of LH-releasing activity). Moreover, combination of example 3 with 10% permethylated  $\alpha$ -CD resulted in an even higher potentiation : the doses of 2.5, 5 and  $10 \mu\text{g/kg p.o.}$ , which remained inactive when example 3 was given alone, yielded a sharp dose-related stimulatory response (Figure 7).

The peptides according to the general formula (I') exert an antagonist activity upon the LH-RH receptors *in vivo*, resulting in particular in the inhibition of ovulation.

The influence of  $\alpha$ -,  $\beta$ - and  $\gamma$ -CD was tested on the activity of antide (an example of LH-RH peptide antagonist) when orally administered by gavage to normally cycling adult female Wistar rats between 1:30 and 3:00 p.m. on the day of proestrus, after at least two full regular estrous cycles as monitored by daily vaginal

smears. The antioviulatory efficacy was checked the next morning, on the day of expected estrus, by looking for ova in the oviduct of treated females. The presence of at least one ovum attested that some degree of spontaneous ovulation did occur, and only the total absence of ovum was considered as effective LH-RH antagonist-induced inhibition of ovulation. Antide was solubilized in a vehicle consisting of 20% (vol/vol) propylene glycol in water already containing 1% bovine albumin, to which 10% (wt/vol) of either  $\alpha$ -,  $\beta$ - or  $\gamma$ -CD was then added. The results of the experiments are summarized in the following Table 4.

Table 4 : Inhibition of ovulation by oral administration of antide

oral formulation	antide ( $\mu\text{g}/\text{rat p.o.}$ )	n ovulations/ N treated rats	percentage of inhibition
vehicle only	0	24/24	0%
vehicle + $\alpha$ -CD (10%)	0	8/8	0%
vehicle only	200	8/8	0%
	400	19/22	14%
	600	5/8	44%
vehicle + $\alpha$ -CD (10%)	200	6/8	25%
	400	6/22	73%
	600	2/8	75%
vehicle + $\beta$ -CD (10%)	400	7/7	0%
vehicle + $\gamma$ -CD (10%)	400	7/7	0%

The vehicle with or without  $\alpha$ -CD had no effect by itself. The threshold effective dose of antide by oral administration was 400  $\mu\text{g}/\text{kg}$  p.o. with only 3 animals out of 22 showing inhibition of ovulation. Beta- and  $\gamma$ -CD had no influence on the minimal activity of antide at this dose level.

However,  $\alpha$ -CD significantly enhanced antide potency from 14% to 73% of inhibition at 400  $\mu\text{g}/\text{kg}$ . The twice lower dose of 200  $\mu\text{g}/\text{kg}$  was even slightly effective (25% of inhibition) in combination with  $\alpha$ -CD 10%. Therefore,  $\alpha$ -CD was able to potentiate the activity of a LH-RH peptide antagonist by oral administration, but not  $\beta$ - or  $\gamma$ -CD.

The oral formulations of the invention can be prepared by methods well known to those skilled in the art, generally as follows : a known amount of a drug is added to an aqueous cyclodextrin solution in sufficient concentration; the drug-cyclodextrin interaction can take place in solution or suspension within minutes or after stirring  
5 for up to 1 week at the desired temperature with or without sonication, depending on the nature of the drug and of the cyclodextrin, and on their respective concentrations. Then, the resulting drug-cyclodextrin combination or complex can be further obtained in a dry form by filtration, centrifugation, evaporation or sublimation.

10 By way of illustration, the example combinations of LH-RH analogues with  $\alpha$ -CD hereafter describe one basic method for the preparation of the formulations according to the invention in solution, notwithstanding their further processing to any appropriate dry form that will take advantage of the same potentiating properties.

Such formulations may further comprise, one or several other  
15 pharmaceutically appropriate excipients for oral administration such as lactose, fructose, glucose, sucrose, compressible sugar, saccharin, povidone, crospovidone, magnesium stearate, kaolin, bentonite, colloidal silica, mannitol, sorbitol, starch and its derivatives, microcrystalline or powdered cellulose, methylcellulose, carboxymethylcellulose, ethylcellulose or other chemically modified celluloses, other  
20 cyclodextrins, maltodextrin, - dextrates, dextrin, dextrose, alginates, pectins, pectates, sorbitan esters, polysorbate 80, chitosan, guar or xanthan gums, mono-, di- or tri-ethanolamine, oleic acid or ethyl oleate, stearic acid, water, liquid glucose, propylene glycol, lactic acid, malic acid, ethanol, isopropyl myristate or palmitate, glycerin, glyceryl monooleate, glyceryl monostearate, glyceryl palmitostearate,  
25 lecithin, medium or short chain triglycerides, various oils from corn, cottonseed, olive, peanut, sesame or soybean, and the like. These formulations are administered by mouth (or naso-gastric tubing) in various aqueous or non-aqueous solutions or suspensions such as true solutions, syrups, elixirs, mucilages, jellies, gels, milks, magmas, macro-, micro- or nano-emulsions, or in various solid forms  
30 such as compressed, coated, buccal, sublingual, effervescent or molded tablets, hard or soft capsules, pills, troches or cachets. Enteric coatings of usual solid oral dosage forms or of soft capsules containing liquid formulations, and sustained, delayed or programmed gastric, enteric or colonic release forms or devices are preferred means to deliver the active principle.



The main target of LH-RH peptide agonists according to formula (I) is the pituitary gland, but direct actions have been reported on the gonads themselves (testis and ovary), on the thymus and some lymphoid cell lines, and on breast, prostate, pancreatic or nervous system tumors. They exert on any LH-RH sensitive target, either a stimulatory activity by short-term acute or pulsatile administration, or an inhibitory effect by repeated or continuous administrations that induce the desensitization and the down-regulation of LH-RH receptors. In the case of the hypothalamo-pituitary-gonadal axis, prolonged administration results in a so-called "chemical" castration.

10 The main target of LH-RH peptide antagonists according to formula (I') is also the pituitary gland, where they bind to the LH-RH receptors and prevent the activity of endogenous LH-RH. By this mechanism, the pituitary-gonadal axis can be inhibited. The programmed use of LH-RH antagonists can also be taken advantage of to obtain a spontaneous stimulation of the pituitary-gonadal axis at any given time by stopping their administration at an appropriate earlier time point.

15 Therefore, LH-RH agonists or antagonists according to formula (A) are useful in all situations where the actions of LH-RH must be either inhibited, prevented or stimulated. Especially, the peptide analogues of the invention are useful in the treatment of LH-RH-sensitive diseases, namely the diseases where a LH-RH agonist or antagonist action is required.

20 Accordingly, the oral pharmaceutical compositions of the invention can find an appropriate therapeutic use in humans as well as in animals, depending on doses and treatment regimens, in reproductive endocrinology and in the treatment or prevention of sex hormone-dependent benign or malignant tumors ; said treatment or prevention may involve parallel and/or sequential supplementary curative or preventive regimens based on other hormonal or antitumoral agents. LH-RH sensitive sex hormone-independent benign or malignant tumors can also regress upon treatment with the oral pharmaceutical compositions according to the invention, alone or associated with other parallel and/or sequential antitumoral treatments. Immune mechanisms can also be modified by the oral pharmaceutical compositions according to the invention, alone or associated with other parallel and/or sequential treatments based on immuno-modulating or -suppressive agents such as glucocorticoids, cyclosporin, rapamycin, tacrolimus, their derivatives, and the like. The oral pharmaceutical compositions according to the invention are

therefore very valuable in the treatment and prevention of autoimmune diseases, graft rejection or atopic diseases, and in the treatment of benign or malignant lymphoproliferative disorders.

The oral pharmaceutical compositions according to the invention are especially useful in the inhibition, planning and triggering of ovulation in *in vitro* fertilization programs, and in the treatment of male and female infertility or hypogonadic states. Conversely, they can also be used in male or female contraception or treatment of hypergonadic states. In both cases, said treatments may involve other parallel and/or sequential treatments with sex steroids and/or gonadotrophins. This applies to men and women, but also to wild or domestic animals in uses such as improvement or control of reproductive performance, or as a tool to optimize breeding strategies.

The oral pharmaceutical compositions according to the invention are also especially useful in men to treat advanced prostate cancer, but can also be used as a first line therapy in this indication and in benign prostatic hypertrophy ; in both cases, said treatments may also involve additional parallel and/or sequential treatments based on inhibitors of androgen action, i.e. antiandrogens such as cyproterone acetate, osaterone acetate, chlormadinone acetate, flutamide, nilutamide or bicalutamide and the like, and/or on 5 $\alpha$ -reductase inhibitors such as finasteride, epristeride or turosteride and the like, and/or on C<sub>17-20</sub> lyase inhibitors such as abiraterone and the like.

The oral pharmaceutical compositions according to the invention are also especially useful in the treatment or prevention of breast cancer in women and in men, especially estrogen receptor positive tumors ; said treatment or prevention may involve parallel or sequential supplementary curative or preventive regimens based on antiestrogens such as tamoxifen, raloxifen or droloxifen and the like, and/or on aromatase inhibitors such as atamestane, formestane, letrozole, anastrozole and the like, and/or on C<sub>17-20</sub> lyase inhibitors such as abiraterone and the like. The oral pharmaceutical compositions according to the invention are also very useful in the treatment or prevention of certain estrogen receptor negative tumors that respond to the direct effects of LH-RH analogues or indirectly to their gonadal suppressive activity.

Other gynecological conditions, such as endometrial hyperplasia, leiomyoma, adenomyoma, endometriosis, polycystic ovary syndrome, hirsutism and benign

breast disease (pain, cysts or fibrosis), can also be prevented by or benefit from treatment with the oral pharmaceutical compositions according to the invention ; said treatment or prevention may involve additional parallel and/or sequential curative or preventive treatments based on antiestrogens (cited above), progestins  
5 such as cyproterone acetate, osaterone acetate, chlormadinone acetate, norgestrol acetate, promegestone, demegestone, trimegestone and the like, and/or their contraceptive or post-menopausal replacement combination formulations with estrogens such as estradiol or ethynylestradiol. The oral compositions of the invention can also interfere with gestation by inducing abortion  
10 or by triggering labor ; in this case they may also be used in parallel or in sequence with treatments based on estrogens (cited above), antiprogestins such as mifepristone and/or prostaglandin analogs such as sulprostone.

Similar indications can be encountered in veterinary medicine for male or female domestic or wild animals that may require the use of pharmaceutical  
15 compositions according to the invention.

A further aspect of the invention relates to a method of treating and/or preventing the above diseases which comprises orally administering to patients or animals in need thereof a pharmaceutical composition according to the invention, said composition comprising an effective amount of a LH-RH peptide analogue as  
20 previously defined in combination with  $\alpha$ -cyclodextrin or a derivative thereof. Said method may comprise the further administration of at least one of the active principles mentioned above such as for example a hormonal agent, an antitumoral agent, an immuno-modulating or -suppressive agent, a sex steroid, a gonadotrophin, an inhibitor of androgen action, a  $5\alpha$ -reductase inhibitor, a  $C_{17-20}$   
25 lyase inhibitor, an antiestrogen, an aromatase inhibitor, a progestin, an estrogen, an antiprogestin or a prostaglandin analogue, said further administration being parallel, sequential or over a period of time.

The unit dose of oral administration of LH-RH peptide analogues according to formula (A) may range from 0.1 to 100 mg per human patient, from one to 16 times  
30 per day (in the case of pulsatile administration), in combination with at least an equimolar amount of  $\alpha$ -CD or its derivatives and up to the total remaining part of the oral formulation.

All the above-mentioned oral pharmaceutical compositions may additionally contain one or several proteases inhibitors, and/or one or several other absorption enhancers.

5 Examples of preparations of leuprorelin, triptorelin, goserelin, deslorelin and examples 1 to 6 in combination with 100 mM  $\alpha$ -CD in solution

On each experimental day, solutions of  $\alpha$ -CD were freshly prepared by dissolving 9.72 g in 100 ml of pure water, or 4.86 g in 50 ml, for 1 hour at room temperature with gentle magnetic stirring; meanwhile, an appropriate volume of each LH-RH analogue was taken from thawed individual stock vials containing 50  
10  $\mu$ g of net peptide in 50  $\mu$ l of phosphate-buffered saline containing 0.1% bovine serum albumin, to make 20 nmoles (24.2  $\mu$ l for LEU, 26.2  $\mu$ l for TRI, 23.4  $\mu$ l for GOS, 25.4  $\mu$ l for DES, 24.7  $\mu$ l for example 1, 23.6  $\mu$ l for example 2, 24.5  $\mu$ l for example 3, 25.1  $\mu$ l for example 4, 26.5  $\mu$ l for example 5 and 23.4  $\mu$ l for example 6) and put in a 10 ml gauged flask. Then, the  $\alpha$ -CD solution was added to fill the flask  
15 up to 10 ml to make a 2 nmol/ml solution of which 1ml was administered by oral gavage to each rat.

Examples of preparation of formulations of example 2 in combination with 5%, 10% or 14%  $\alpha$ -CD solutions

On each experimental day, 45  $\mu$ l of one thawed individual vial containing 50  
20  $\mu$ g of net example 2 in 50  $\mu$ l of phosphate-buffered saline containing 0.1 % bovine serum albumin, were diluted in 36 ml of distilled water to give a 1.25  $\mu$ g/ml solution from which three fractions of 3.8 ml were taken; then, 190, 380 or 532 mg of  $\alpha$ -CD were added to each fraction to give a concentration of 5%, 10% or 14%, respectively. After overnight magnetic stirring at room temperature, each solution  
25 was given to rats by oral gavage in a 4 ml/kg volume to administer the same dose of 5  $\mu$ g/kg of example 2 without or with increasing concentrations of  $\alpha$ -CD.

Examples of preparation of formulations for oral administration of example 3 in combination with  $\alpha$ -CD derivatives

On each experimental day, frozen vials containing 50  $\mu$ g of net example 3 in  
30 50  $\mu$ l of phosphate-buffered saline containing 0.1% bovine serum albumin were thawed and diluted by half with an equal volume of the same fresh bovine serum albumin solution. Then, 12.5  $\mu$ l of this 0.5  $\mu$ g/ $\mu$ l solution were added to 5 ml of aqueous vehicle for oral administration (with or without  $\alpha$ -CD derivative) to give a

final formulation containing 1.25  $\mu\text{g/ml}$  of example 3 to be administered by gavage under a volume of 4 ml/kg, after gentle magnetic stirring overnight.

The solutions of  $\alpha$ -CD derivatives were prepared by weighing the appropriate amount to put in 10 ml gauged flasks to fill up with water : 5 g of carboxymethylated  $\alpha$ -CD (50%), 3 g of methylated  $\alpha$ -CD (30%), 3 g of phosphated  $\alpha$ -CD (30%) or 1 or 1.5 g of permethylated  $\alpha$ -CD (10 or 15%).

Appropriate volumes of convenient dilutions of the 50  $\mu\text{g}/50 \mu\text{l}$  stock vials of net example 3 were added to 10% solutions of  $\alpha$ -CD or permethylated  $\alpha$ -CD in water to obtain the dose range described in figure 7.

10      Examples of preparations of formulations for oral administration of antide in combination with  $\alpha$ -,  $\beta$ - or  $\gamma$ -CD

Each 5 mg powder vial of antide (from Bachem, Bubendorf, Switzerland) containing 4.2434 mg net peptide was dissolved in a mixture of 2.122 ml propylene glycol with 8.487 ml water containing 0.1% bovine albumin. To each 10.609 ml solution of antide (400  $\mu\text{g/ml}$ ), 1.061 g of either  $\alpha$ -,  $\beta$ - or  $\gamma$ -CD was directly added to obtain a 10% concentration. Each female rat received the same volume of 1 ml of test formulation by gavage.

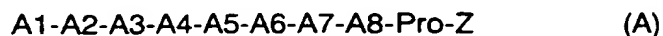
The same volume of administration was used for the doses of 200 and 600  $\mu\text{g/rat}$ . The appropriate concentrations of antide to be administered (200 and 600  $\mu\text{g/ml}$ ) were respectively obtained by diluting by half the 400  $\mu\text{g/ml}$  solution with the same [20% vol. propylene glycol/80% vol. albuminated water/10% wt  $\alpha$ -CD] mixture, and by dissolving other 5 mg powder vials in 1.415 ml propylene glycol with 5.658 ml water already containing 0.1% bovine albumin to which 0.707 mg of  $\alpha$ -CD was finally added.

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## CLAIMS

1. Use of  $\alpha$ -cyclodextrin or a derivative thereof for the preparation of a pharmaceutical composition for the oral administration of a LH-RH peptide analogue or one of its pharmaceutically acceptable salt.

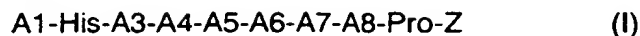
2. Use according to claim 1 wherein said peptide analogue has the formula (SEQ ID N° : 1) :



in which :

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an optionally substituted and/or acylated aromatic D-amino acid;
- A2 is a direct bond ; His ; or an optionally substituted aromatic D-amino acid;
- A3 is an optionally substituted aromatic L- or D-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu<sup>t</sup>), Ser(OBzl) or Thr;
- A5 is an optionally substituted aromatic L-amino acid or an optionally substituted basic L- or D-amino acid ;
- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu<sup>t</sup>) ; D-Asp(OBu<sup>t</sup>) ; D-Glu(OBu<sup>t</sup>) ; D-Thr(OBu<sup>t</sup>) ; D-Cys(OBu<sup>t</sup>) ; D-Ser(OR<sub>1</sub>) where R<sub>1</sub> is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C<sub>1</sub>-C<sub>6</sub>)alkyl, a (C<sub>2</sub>-C<sub>7</sub>)acyl or a benzyl group ; an aliphatic D-amino acid with a (C<sub>1</sub>-C<sub>6</sub>)alkyl or a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic L- or D-amino acid;
- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C<sub>1</sub>-C<sub>4</sub>)alkyl group- optionally substituted by one or several fluorine atoms ;
- A8 is an optionally substituted basic L- or D-amino acid;
- Z is GlyNH<sub>2</sub> ; D-AlaNH<sub>2</sub> ; azaGlyNH<sub>2</sub> ; or a group -NHR<sub>2</sub> where R<sub>2</sub> is a (C<sub>1</sub>-C<sub>4</sub>)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

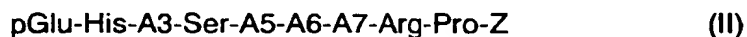
3. Use according to claim 2 wherein said peptide analogue has the formula (SEQ ID N° : 2) :



in which:

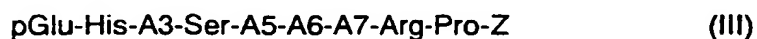
- 5       - A1 is pGlu, Sar or AcSar;
- A3 is an optionally substituted aromatic L-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu<sup>h</sup>), Ser(OBzl) or Thr;
- A5 is an optionally substituted aromatic L-amino acid ;
- A6 is Gly ; D-Pro ; (S)-spirolactam-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu<sup>h</sup>) ; D-Asp(OBu<sup>h</sup>) ; D-Glu(OBu<sup>h</sup>) ; D-Thr(OBu<sup>h</sup>) ; D-Cys(OBu<sup>h</sup>) ; D-Ser(OR<sub>1</sub>) where R<sub>1</sub> is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C<sub>1</sub>-C<sub>6</sub>)alkyl or a benzyl group ; an aliphatic D-amino acid with a (C<sub>1</sub>-C<sub>8</sub>)alkyl or a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ;
- 10       D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic D-amino acid;
- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C<sub>1</sub>-C<sub>4</sub>)alkyl group optionally substituted by one or several fluorine atoms;
- 20       - A8 is an optionally substituted basic L-amino acid;
- Z is GlyNH<sub>2</sub> ; azaGlyNH<sub>2</sub> ; or a group -NHR<sub>2</sub> where R<sub>2</sub> is a (C<sub>1</sub>-C<sub>4</sub>)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

25       4. Use according to claim 3 wherein said peptide analogue has the formula (SEQ ID N° : 3) :



in which A7 is Leu, Ile, Nle, Hol, Npg, Cha or Ada, which may be N-alpha-substituted by a methyl or ethyl group optionally substituted by one or several  
30       fluorine atoms.

5. Use according to claim 3 wherein said peptide analogue has the formula (SEQ ID N° : 4) :



in which:

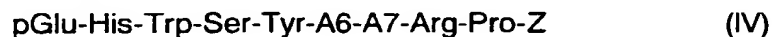
- A3 and A5 are each independently Phe, Tyr, Trp, 2MeTrp, HPhe, HTyr, Nal, 1Nal, Bal, Pal, 4Pal, or pClPhe ;

- A6 is (S)-spirolactam-Pro ; Gly; D-Pro ; D-Ser(OBu<sup>t</sup>) ; D-Asp(OBu<sup>t</sup>) ; D-Glu(OBu<sup>t</sup>) ; D-Thr(OBu<sup>t</sup>) ; D-Cys(OBu<sup>t</sup>) ; D-His or D-His(Bzl) ; D-Ala, D-Leu, D-Tle, D-Nle, D-Hol, D-Npg or D-Cha ; D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-Bal, D-Pal, D-4Pal, or D-pClPhe; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or D-APhe optionally substituted by an aminotriazolyl group ;

- A7 is Leu, Npg or Cha, which may be N-alpha-substituted by a methyl group;

- Z is GlyNH<sub>2</sub> ; azaGlyNH<sub>2</sub> or -NC<sub>2</sub>H<sub>5</sub>.

6. Use according to claim 3 wherein said peptide analogue has the formula (SEQ ID N° : 5) :



in which:

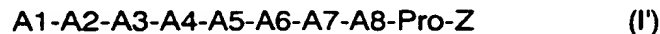
- A6 is (S)-spirolactam-Pro, D-Leu, D-Ala, D-Nal, D-Phe, D-Ser(OBu<sup>t</sup>) or D-Trp;

- A7 is Leu, MeLeu, Npg or MeNpg;

- Z is GlyNH<sub>2</sub> ; azaGlyNH<sub>2</sub> or -NC<sub>2</sub>H<sub>5</sub>.

7. Use according to one of claims 3 to 6 wherein the peptide analogue is selected from the group consisting of leuprorelin, [Npg<sup>7</sup>]-leuprorelin, triptorelin, [Npg<sup>7</sup>]-triptorelin, goserelin, [Npg<sup>7</sup>]-goserelin, buserelin and [Npg<sup>7</sup>]-buserelin.

8. Use according to claim 2 wherein said peptide analogue has the formula (SEQ ID N° : 6) :



in which:

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an optionally substituted and/or acylated aromatic D-amino acid;

- A2 is a direct bond or an optionally substituted aromatic D-amino acid;

- A3 is an optionally substituted aromatic L- or D-amino acid;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu<sup>t</sup>), Ser(OBzl) or Thr;

- A5 is an optionally substituted aromatic L-amino acid or an optionally substituted basic L- or D-amino acid;



- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu<sup>1</sup>) ; D-Asp(OBu<sup>1</sup>) ; D-Glu(OBu<sup>1</sup>) ; D-Thr(O-Bu<sup>1</sup>) ; D-Cys(O-Bu<sup>1</sup>) ; D-Ser(O-R<sub>1</sub>) where R<sub>1</sub> is a sugar moiety ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic L- or D-amino acid;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C<sub>1</sub>-C<sub>4</sub>)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is an optionally substituted basic L- or D-amino acid;

- Z is GlyNH<sub>2</sub> or D-AlaNH<sub>2</sub>.

9. Use according to claim 8 wherein the peptide analogue has the formula (SEQ ID N° : 7):

Ac-D-Nal-D-pClPhe-D-Pal-Ser-A5-A6-A7-A8-Pro-D-AlaNH<sub>2</sub> (II')

in which :

- A5 is Tyr, HTyr, MeTyr, MeHTyr, NicLys or IprLys;

- A6 is (S)-spirolactam-Pro, D-Arg, D-NicLys, D-IprLys, D-Cit, D-HCit or D-Asn;

- A7 is Leu, MeLeu, Npg or MeNpg;

- A8 is Arg, NicLys or IprLys.

10. Use according to claim 8 or 9 wherein the peptide analogue is selected from the group consisting of antide, [Npg<sup>7</sup>]-antide, cetorelix, [Npg<sup>7</sup>]-cetorelix, abarelix and [Npg<sup>7</sup>]-abarelix.

11. Use according to one of claims 1 to 10 wherein the  $\alpha$ -cyclodextrin derivative is selected from the group consisting of methylated  $\alpha$ -cyclodextrin, hexakis(2,3,6-tri-O-methyl)- $\alpha$ -cyclodextrin, carboxymethylated  $\alpha$ -cyclodextrin and phosphated  $\alpha$ -cyclodextrin.

12. Use according to one of claims 1 to 11 of  $\alpha$ -cyclodextrin or hexakis(2,3,6-tri-O-methyl)- $\alpha$ -cyclodextrin.

13. Use according to one of claims 1 to 12 wherein the pharmaceutical composition is intended to be delivered to the gastrointestinal tract.

14. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment of infertility, hypogonadic or hypergonadic states.

5 15. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is a contraceptive agent.

16. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of prostate cancer or benign prostatic hypertrophy.

10 17. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of breast cancer.

18. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of sex hormone-related benign or malignant tumors.

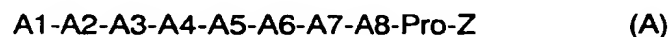
15 19. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of sex hormone-independent but LH-RH sensitive benign or malignant tumors.

20. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of benign or malignant lymphoproliferative disorders.

20 21. A pharmaceutical composition for the gastrointestinal delivery by oral administration of a LH-RH peptide analogue which comprises a therapeutically effective amount of said peptide analogue in combination with  $\alpha$ -cyclodextrin or a derivative thereof.

25 22. The pharmaceutical composition according to claim 21 which further comprises excipients suitable for the gastrointestinal delivery of the peptide analogue.

23. The pharmaceutical composition according to claim 21 or 22 wherein said peptide analogue has the formula (SEQ ID N° : 1) :



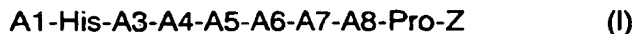
30 in which :

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an optionally substituted and/or acylated aromatic D-amino acid;

- A2 is a direct bond ; His ; or an optionally substituted aromatic D-amino acid;

- A3 is an optionally substituted aromatic L- or D-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu<sup>t</sup>), Ser(OBzl) or Thr;
- A5 is an optionally substituted aromatic L-amino acid or an optionally substituted basic L- or D-amino acid;
- 5       - A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu<sup>t</sup>) ; D-Asp(OBu<sup>t</sup>) ; D-Glu(OBu<sup>t</sup>) ; D-Thr(OBu<sup>t</sup>) ; D-Cys(OBu<sup>t</sup>) ; D-Ser(OR<sub>1</sub>) where R<sub>1</sub> is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C<sub>1</sub>-C<sub>6</sub>)alkyl, a (C<sub>2</sub>-C<sub>7</sub>)acyl or a benzyl group ; an aliphatic D-amino acid with a (C<sub>1</sub>-C<sub>8</sub>)alkyl or a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic L- or D-amino acid;
- 10       - A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C<sub>1</sub>-C<sub>4</sub>)alkyl group optionally substituted by one or several fluorine atoms;
- 15       - A8 is an optionally substituted basic L- or D-amino acid;
- Z is GlyNH<sub>2</sub> ; D-AlaNH<sub>2</sub> ; azaGlyNH<sub>2</sub> ; or a group -NHR<sub>2</sub> where R<sub>2</sub> is a (C<sub>1</sub>-C<sub>4</sub>)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.
- 20

24. The pharmaceutical composition according to claim 23 wherein said peptide analogue has the formula (SEQ ID N° : 2) :



in which:

- 25       - A1 is pGlu, Sar or AcSar;
- A3 is an optionally substituted aromatic L-amino acid ;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu<sup>t</sup>), Ser(OBzl) or Thr;
- A5 is an optionally substituted aromatic L-amino acid ;
- A6 is Gly ; D-Pro ; (S)-spirolactam-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu<sup>t</sup>) ; D-Asp(OBu<sup>t</sup>) ; D-Glu(OBu<sup>t</sup>) ; D-Thr(OBu<sup>t</sup>) ; D-Cys(OBu<sup>t</sup>) ; D-Ser(OR<sub>1</sub>) where R<sub>1</sub> is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C<sub>1</sub>-C<sub>6</sub>)alkyl or a benzyl group ; an aliphatic D-amino acid with a (C<sub>1</sub>-C<sub>8</sub>)alkyl or a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ;
- 30

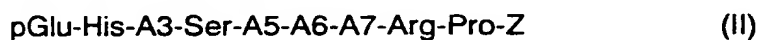
D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic D-amino acid ;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C<sub>1</sub>-C<sub>4</sub>)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is an optionally substituted basic L-amino acid;

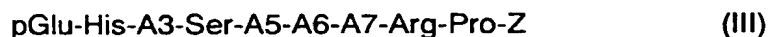
- Z is GlyNH<sub>2</sub> ; azaGlyNH<sub>2</sub> ; or a group -NHR<sub>2</sub> where R<sub>2</sub> is a (C<sub>1</sub>-C<sub>4</sub>)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

25. The pharmaceutical composition according to claim 24 wherein said peptide analogue has the formula (SEQ ID N° : 3) :



in which A7 is Leu, Tle, Nle, Hol, Npg, Cha or Ada, which may be N-alpha-substituted by a methyl or ethyl group optionally substituted by one or several fluorine atoms.

26. The pharmaceutical composition according to claim 24 wherein said peptide analogue has the formula (SEQ ID N° : 4) :



in which:

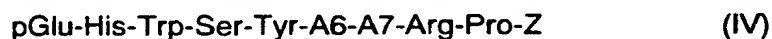
- A3 and A5 are each independently Phe, Tyr, Trp, 2MeTrp, HPhe, HTyr, Nal, 1Nal, Bal, Pal, 4Pal, or pClPhe ;

- A6 is (S)-spirolactam-Pro ; Gly; D-Pro ; D-Ser(OBu<sup>1</sup>) ; D-Asp(OBu<sup>1</sup>) ; D-Glu(OBu<sup>1</sup>) ; D-Thr(OBu<sup>1</sup>) ; D-Cys(OBu<sup>1</sup>) ; D-His or D-His(Bzl) ; D-Ala, D-Leu, D-Tle, D-Nle, D-Hol, D-Npg or D-Cha ; D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-Bal, D-Pal, D-4Pal, or D-pClPhe; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala or D-APhe optionally substituted by an aminotriazolyl group;

- A7 is Leu, Npg or Cha, which may be N-alpha-substituted by a methyl group;

- Z is GlyNH<sub>2</sub>, azaGlyNH<sub>2</sub> or -NC<sub>2</sub>H<sub>5</sub>.

27. The pharmaceutical composition according to claim 24 wherein said peptide analogue has the formula (SEQ ID N° : 5) :



in which:

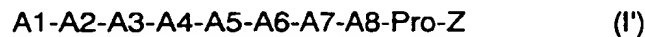
- A6 is (S)-spirolactam-Pro, D-Leu, D-Ala, D-Nal, D-Phe, D-Ser(OBu<sup>t</sup>) or D-Trp;

- A7 is Leu, MeLeu, Npg or MeNpg;

- Z is GlyNH<sub>2</sub>, azaGlyNH<sub>2</sub> or -NC<sub>2</sub>H<sub>5</sub>.

5        28.        The pharmaceutical composition according to one of claims 24 to 27 wherein the peptide analogue is selected from the group consisting of leuprorelin, [Npg<sup>7</sup>]-leuprorelin, triptorelin, [Npg<sup>7</sup>]-triptorelin, goserelin, [Npg<sup>7</sup>]-goserelin, buserelin and [Npg<sup>7</sup>]-buserelin.

10        29.        The pharmaceutical composition according to claim 23 wherein said peptide analogue has the formula (SEQ ID N° : 6) :



in which:

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an optionally substituted and/or acylated aromatic D-amino acid;

- A2 is a direct bond or an optionally substituted aromatic D-amino acid;

- A3 is an optionally substituted aromatic L- or D-amino acid;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu<sup>t</sup>), Ser(OBzl) or Thr;

20        - A5 is an optionally substituted aromatic L-amino acid or an optionally substituted basic L- or D-amino acid;

25        - A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu<sup>t</sup>) ; D-Asp(OBu<sup>t</sup>) ; D-Glu(O-Bu<sup>t</sup>) ; D-Thr(O-Bu<sup>t</sup>) ; D-Cys(O-Bu<sup>t</sup>) ; D-Ser(O-R<sub>1</sub>) where R<sub>1</sub> is a sugar moiety ; an aliphatic D-amino acid with a (C<sub>1</sub>-C<sub>6</sub>)alkyl or a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic L- or D-amino acid;

30        - A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C<sub>1</sub>-C<sub>4</sub>)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is an optionally substituted basic L- or D-amino acid;

- Z is GlyNH<sub>2</sub> or D-AlaNH<sub>2</sub>.

30        30.        The pharmaceutical composition according to claim 29 wherein the peptide analogue has the formula (SEQ ID N° : 7):

Ac-D-Nal-D-pCIPhe-D-Pal-Ser-A5-A6-A7-A8-Pro-D-AlaNH<sub>2</sub> (II')

in which :

- A5 is Tyr, HTyr, MeTyr, MeHTyr, NicLys or IprLys;
- A6 is (S)-spirolactam-Pro, D-Arg, D-NicLys, D-IprLys, D-Cit, D-HCit or D-Asn;
- A7 is Leu, MeLeu, Npg or MeNpg;
- A8 is Arg, NicLys or IprLys.

31. The pharmaceutical composition according to claim 29 or 30 wherein the peptide analogue is selected from the group consisting of antide, [Npg<sup>7</sup>]-antide, cetorelix, [Npg<sup>7</sup>]-cetorelix, abarelix and [Npg<sup>7</sup>]-abarelix.

32. The pharmaceutical composition according to one of claims 21 to 31 wherein the  $\alpha$ -cyclodextrin derivative is selected from the group consisting of methylated  $\alpha$ -cyclodextrin, hexakis(2,3,6-tri-O-methyl)- $\alpha$ -cyclodextrin, carboxymethylated  $\alpha$ -cyclodextrin and phosphated  $\alpha$ -cyclodextrin.

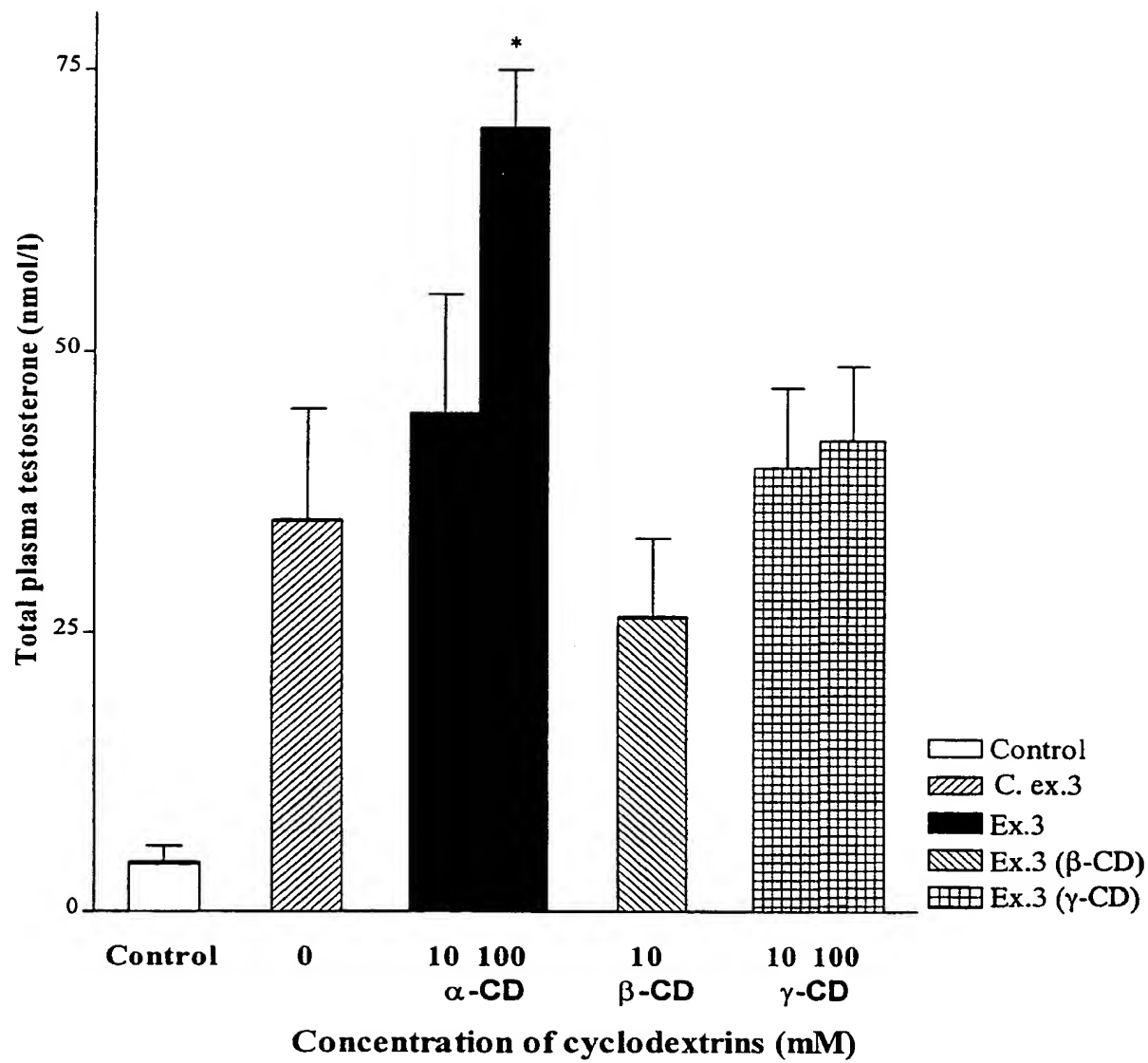
33. The pharmaceutical composition according to one of claims 21 to 32 comprising  $\alpha$ -cyclodextrin or hexakis(2,3,6-tri-O-methyl)- $\alpha$ -cyclodextrin in combination with the LH-RH peptide analogue.

34. The pharmaceutical composition according to one of claims 21 to 33 which further comprises a protease inhibitor and/or an absorption enhancer.

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FIG.1



\*p < 0.05 vs C. ex.3 in vehicle

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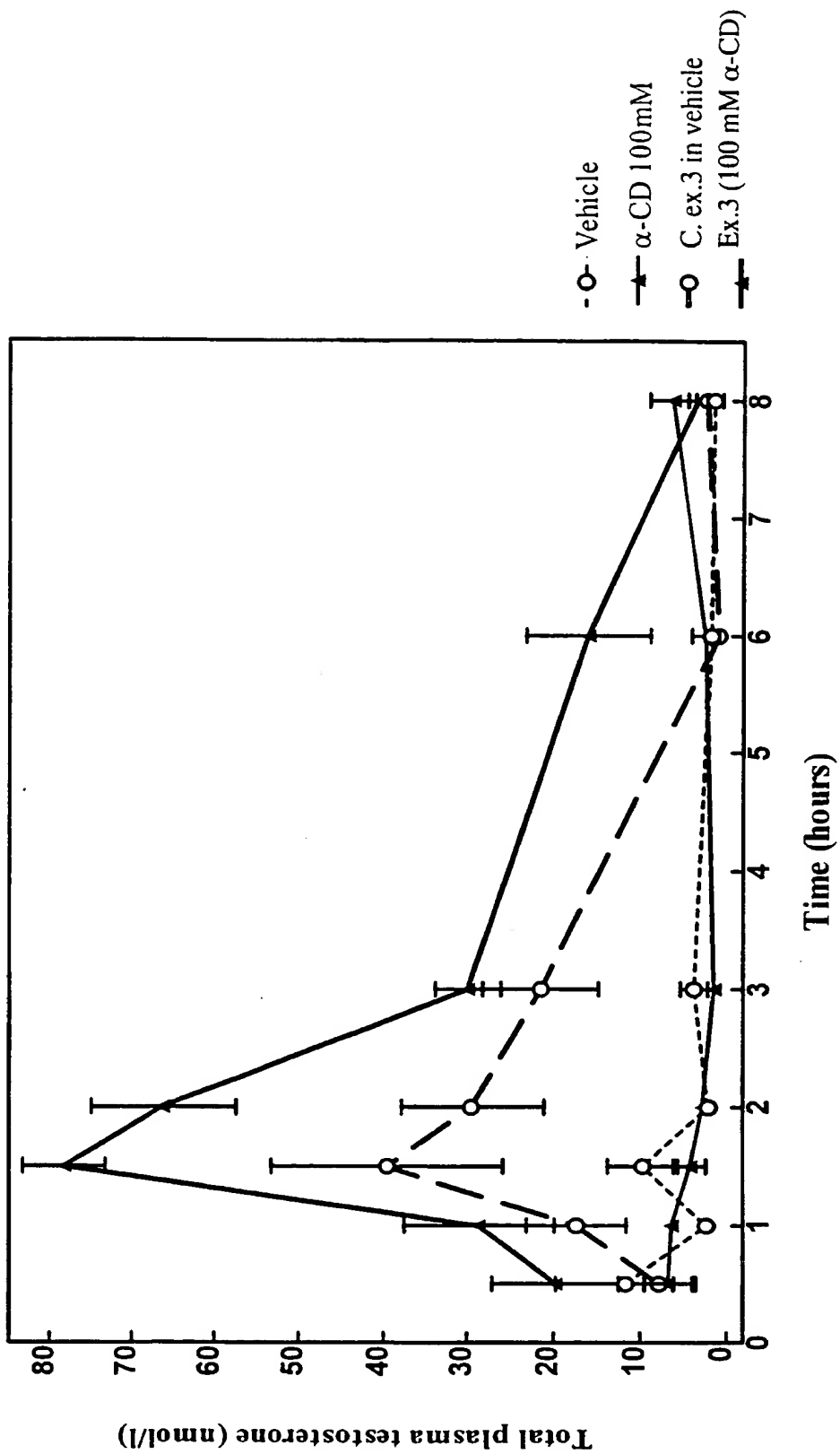


FIG.2



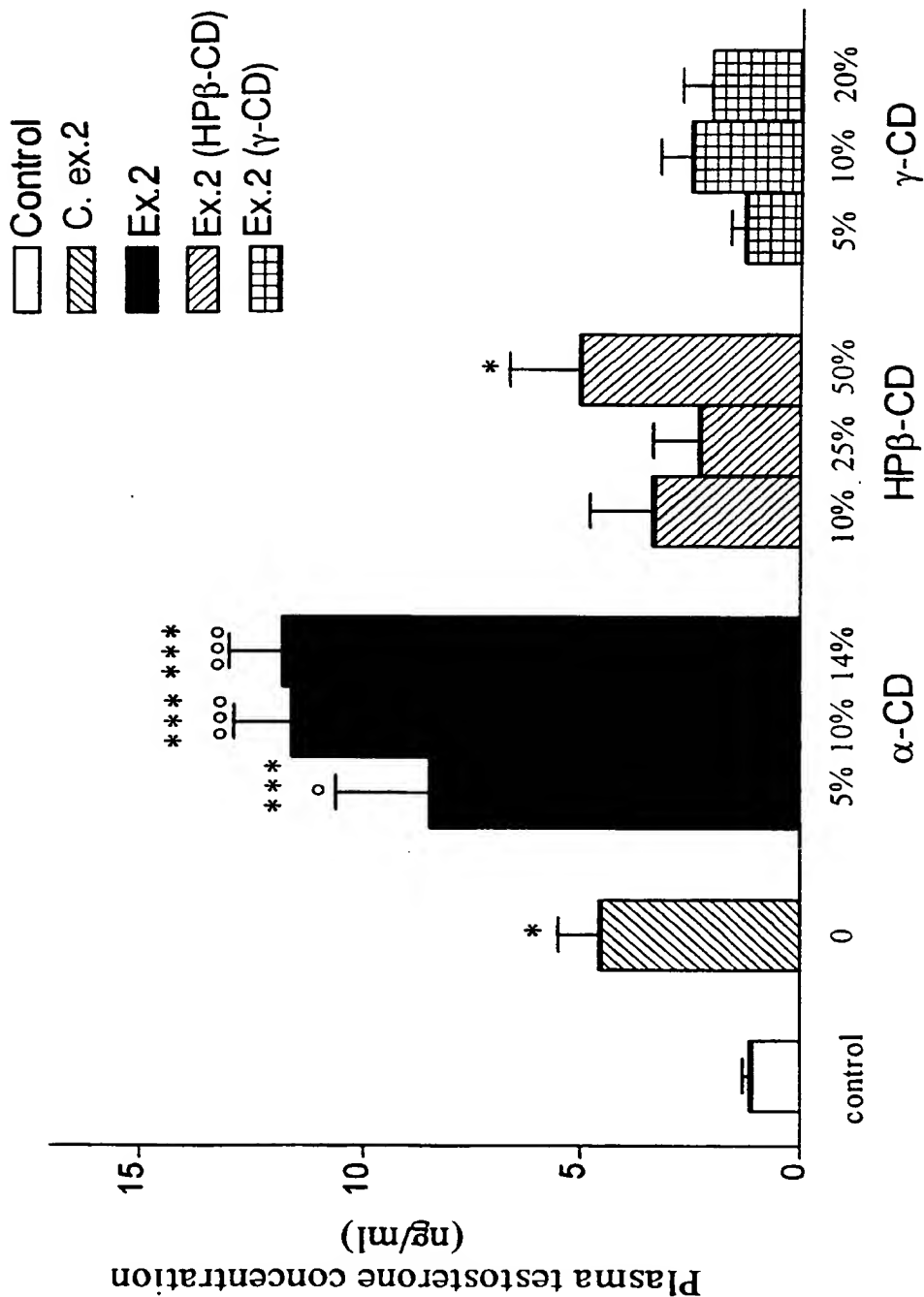
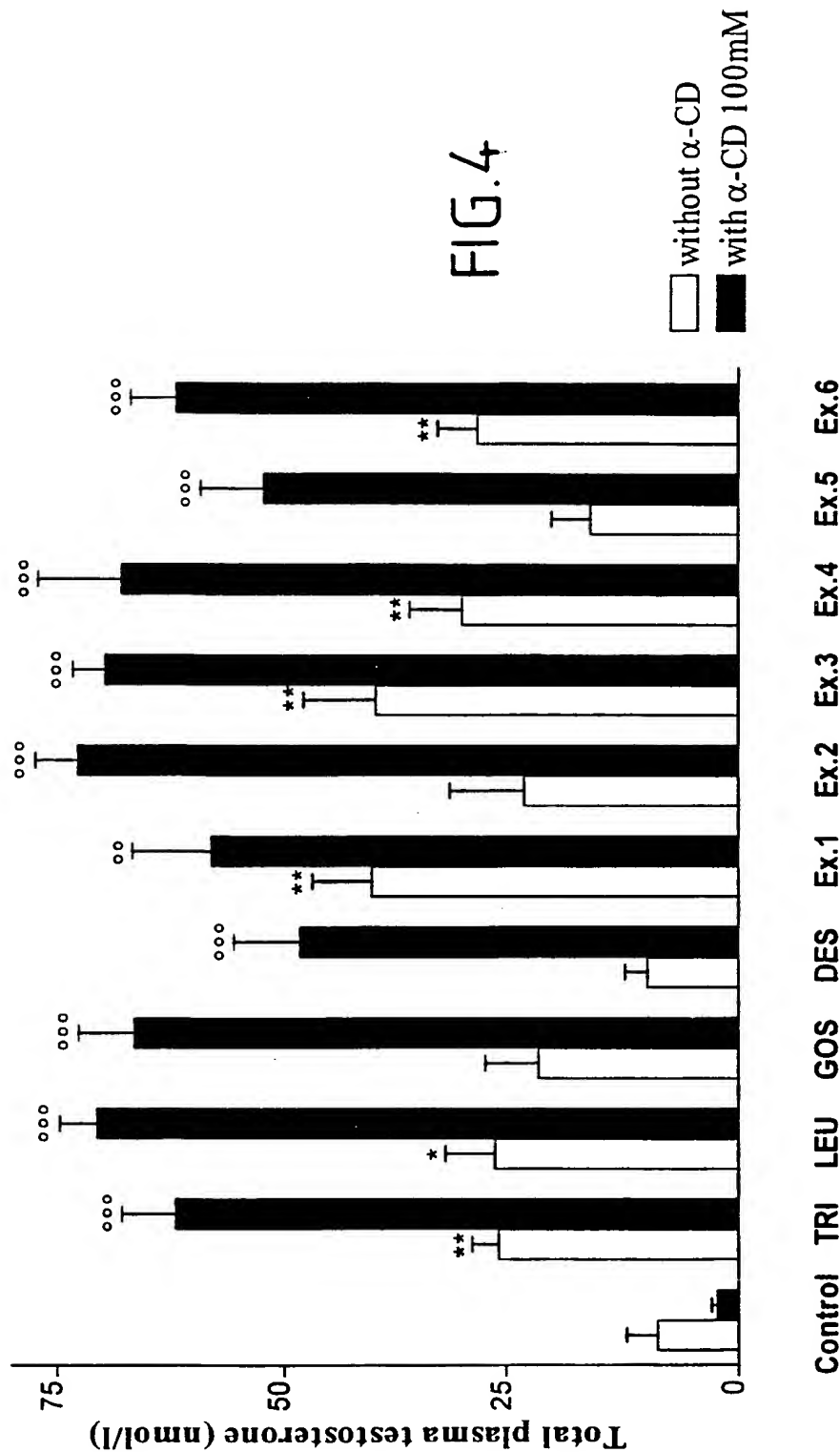


FIG.3

\* p<0.05, \*\*\* p<0.001 vs control group  
° p<0.05, °°° p<0.001 vs C. ex.2 in vehicle

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\*  $p < 0.05$ , \*\*  $p < 0.01$  vs control without  $\alpha$ -CD  
\*\*\*  $p < 0.001$ , \*\*\*\*  $p < 0.0001$  vs control  $\alpha$ -CD

5/7

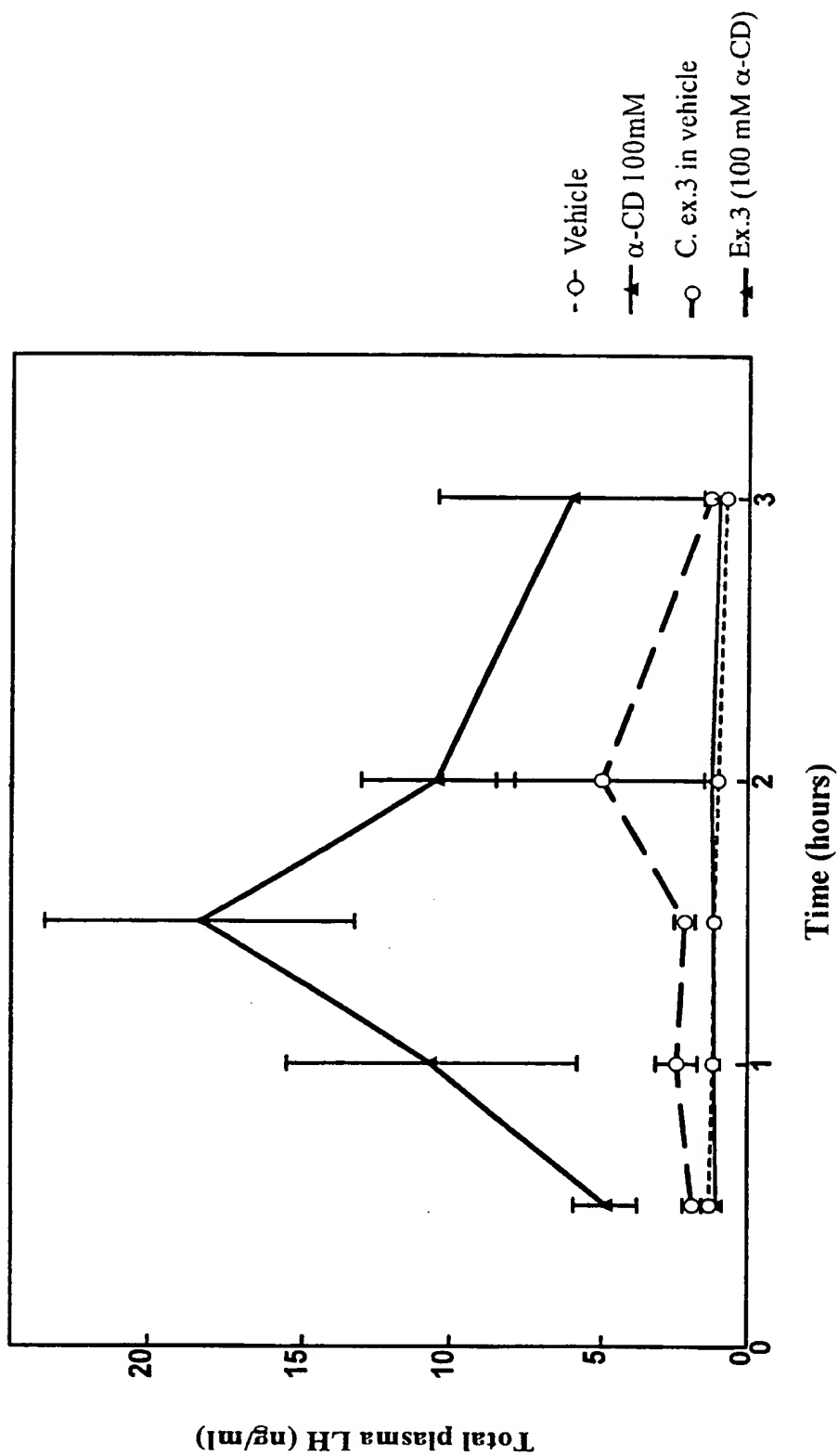
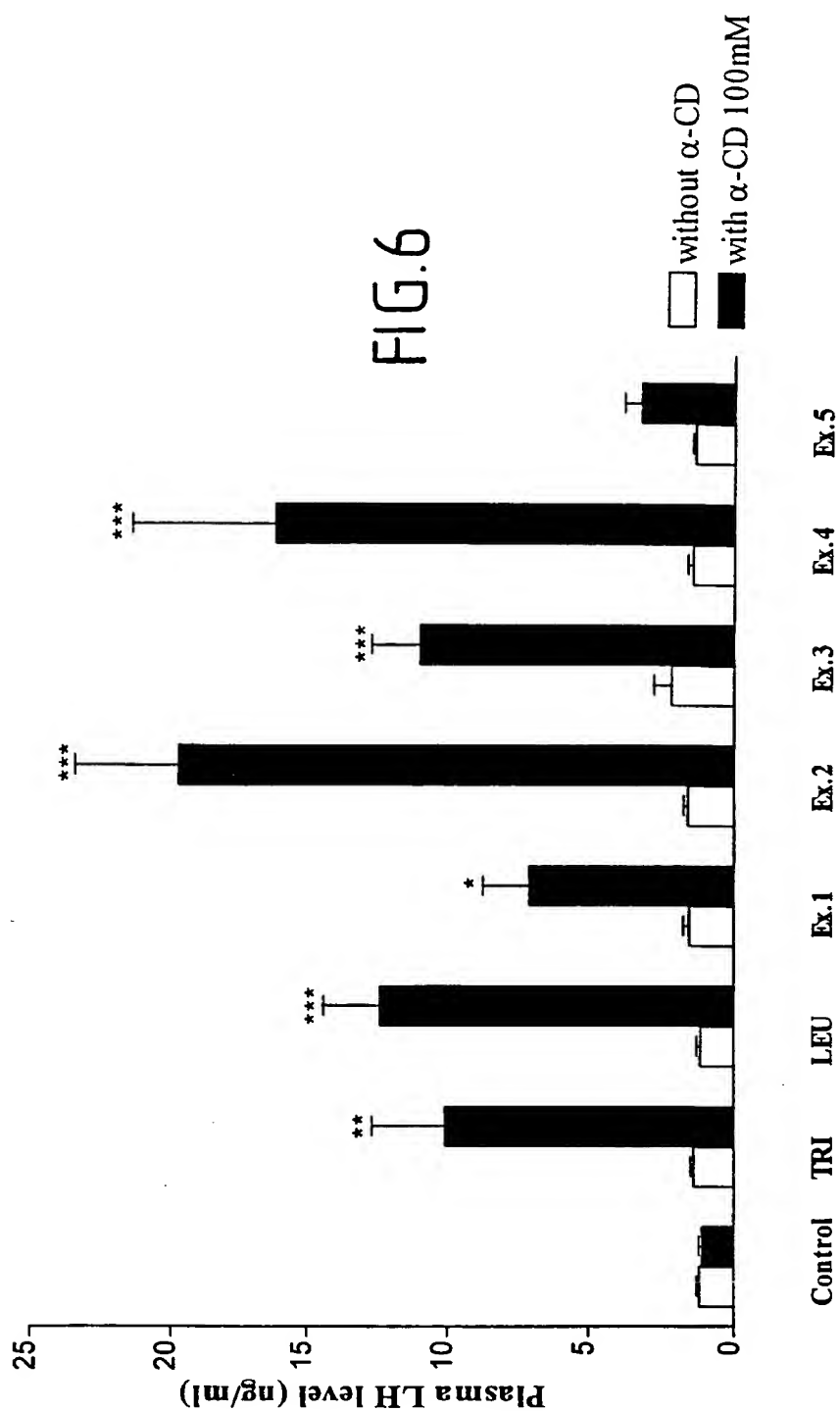


FIG.5

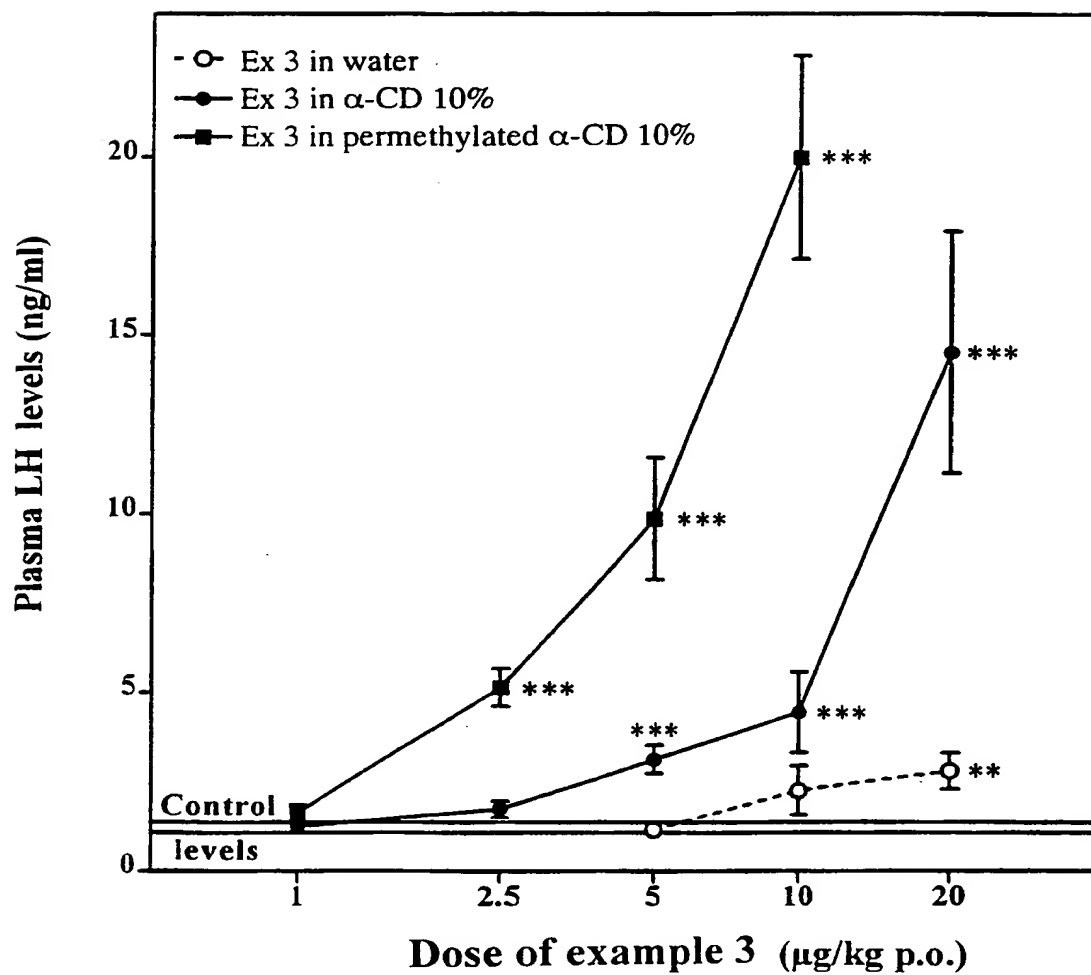
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\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  vs control  $\alpha$ -CD

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FIG.7



(\*\*p<0.01;\*\*\*p<0.001 vs. control unstimulated LH levels)

## INTERNATIONAL SEARCH REPORT

 Int. Application No  
 PCT/EP 99/07389

 A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 A61K38/09 A61K47/40

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 0 308 181 A (NOVO INDUSTRI AS) 22 March 1989 (1989-03-22) abstract  column 1, line 3 - line 9 column 3, line 8 - line 37 column 3, line 54 - column 4, line 22 column 4, line 59 - line 64 claims 1,5-7,12,13 — —/—	1,11-13, 21,32-34 2-12, 14-20, 22-33

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

21 January 2000

Date of mailing of the international search report

28/01/2000

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Stein, A

## INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/EP 99/07389

## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 842 946 A (THERAMEX) 20 May 1998 (1998-05-20) cited in the application abstract page 3, line 38 -page 6, line 45 page 11, line 15 -page 12, line 46 page 20, line 30 -page 27, line 20 claims 1-20	2-10, 14-20, 22-31
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X	US 4 659 696 A (HIRAI SHIN-ICHIRO ET AL) 21 April 1987 (1987-04-21) abstract column 1, line 19 - line 42 column 3, line 12 - line 48 column 4, line 22 - line 41 column 6, line 42 - line 64 column 9, line 15 - line 49 column 10, line 64 -column 11, line 19 examples 3-5,9,12 claims 1,2,5,6,8,10-13,16,19,21	1-7,13, 21-28
X	EP 0 839 525 A (TAKEDA CHEMICAL INDUSTRIES LTD) 6 May 1998 (1998-05-06) page 2, line 49 -page 3, line 20 page 5, line 6 -page 7, line 26 page 9, line 43 - line 51 page 10, line 27 - line 33 page 13, line 41 - line 49 claims 10-16	1-7,13, 22-28,33

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/EP 99/07389

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# PATENT COOPERATION TREATY

## PCT

REC'D 26 OCT 2000

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT PCT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1H200580/0005W00/MN	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/07389	International filing date (day/month/year) 23/09/1999	Priority date (day/month/year) 30/09/1998
International Patent Classification (IPC) or national classification and IPC A61K38/09		
Applicant LABORATOIRE THERAMEX et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of <sup>8</sup>15 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  28/03/2000	Date of completion of this report  24.10.2000
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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/07389

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-22 as originally filed

**Claims, No.:**

1-34 as originally filed

35-62 as received on 04/10/2000 with letter of 02/10/2000

**Drawings, sheets:**

1/7-7/7 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 35-62 (industrial applicability).

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/07389

because:

- ☒ the said international application, or the said claims Nos. 35-62 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	1-62
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-62
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-34; see separate sheet for claims 35-62
	No:	Claims	-

**2. Citations and explanations**

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

- 1- Claims 35-62 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

- 2- Reference is made to the following documents:

D1: EP-A-0 308 181 (NOVO INDUSTRI AS) 22 March 1989 (1989-03-22)

D2: EP-A-0 839 525 (TAKEDA CHEMICAL INDUSTRIES LTD) 6 May 1998 (1998-05-06)

**NOVELTY - Art. 33 (1) and (2) PCT**

- 3- **Claims 1-62 appear to be novel in the light of the prior art cited in the search report, for the reasons stated below:**

3.1- None of the prior art documents cited in the search report explicitly discloses a composition comprising  $\alpha$ -cyclodextrin or a derivative thereof and a LH-RH peptide analogue or one of its pharmaceutically acceptable salts.

3.2- D1 discloses a preparation for non enteral trans-mucosal drug delivery, including oral mucosal (which is different from the oral administration of the present application which is intended to be delivered in the gastrointestinal tract - see e. g. claim 13 of the present application), comprising a pharmaceutically active agent and an absorption enhancer vehicle (c 3 lines 17- 25).

A preferred group of absorption enhancers mentioned in D1 comprises (among others)  $\alpha$ -cyclodextrin (c 3 lines 54-60).

The active agent of D1 is a polypeptide (c 4 line 2) such as (among others) the luteinizing hormone releasing hormone (c 4 line 16). However, D1 does not mention LH-RH peptide analogs (as defined in p 4 lines 29-30 of the present application).

D1 does not explicitly disclose the specific selection of an  $\alpha$ -cyclodextrin or a derivative thereof combined with a LH-RH peptide analogue or one of its pharmaceutically acceptable salts and claims 1-62 can therefore be considered as being novel over D1.

3.3- D2 discloses a sustained-release formulation comprising a polymer of lactic acid and LHRH agonists and antagonists as physiologically active substance.

In addition D2 mentions that stabilizers such as (among others)  $\alpha$ -cyclodextrin and a derivative thereof may be added (p 10 lines 27-33).

Finally, D2 discloses (among others) an oral preparation of the above mentioned composition (p 13 lines 41-49).

D2 does not explicitly disclose the specific combination of an  $\alpha$ -cyclodextrin or a derivative thereof and a LH-RH peptide analogue or one of its pharmaceutically acceptable salts.

Claims 1-62 can therefore be considered as being novel over D2.

**INVENTIVE STEP - Art. (1) and (3) PCT**

- 4- The problem posed in the present application is to provide formulations which enable the gastrointestinal delivery by oral administration of LH-RH peptide analogs.
- 4.1- The solution proposed in the present application is to combine the LH-RH peptide analogs with  $\alpha$ -cyclodextrin or its derivatives.
- 4.2- D1 and D2, relating to compositions for oral administration represent the closest prior art.
- 4.3- Nothing in D1 and D2 suggests that the activity of LHRH peptide analogues when delivered gastrointestinally by oral administration would be enhanced when said peptide is administered with  $\alpha$ -cyclodextrin.
- 4.4- Hence, claims 1-62 can be considered as being inventive.

**INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT**

- 5- For the assessment of the present claims 35-62 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
- 5.1- Claims 1-34 appear to be industrially applicable.